

On-Demand Therapy for Parkinson's Disease

Peter Lin, MD

Movement Disorders Specialist, Los Gatos

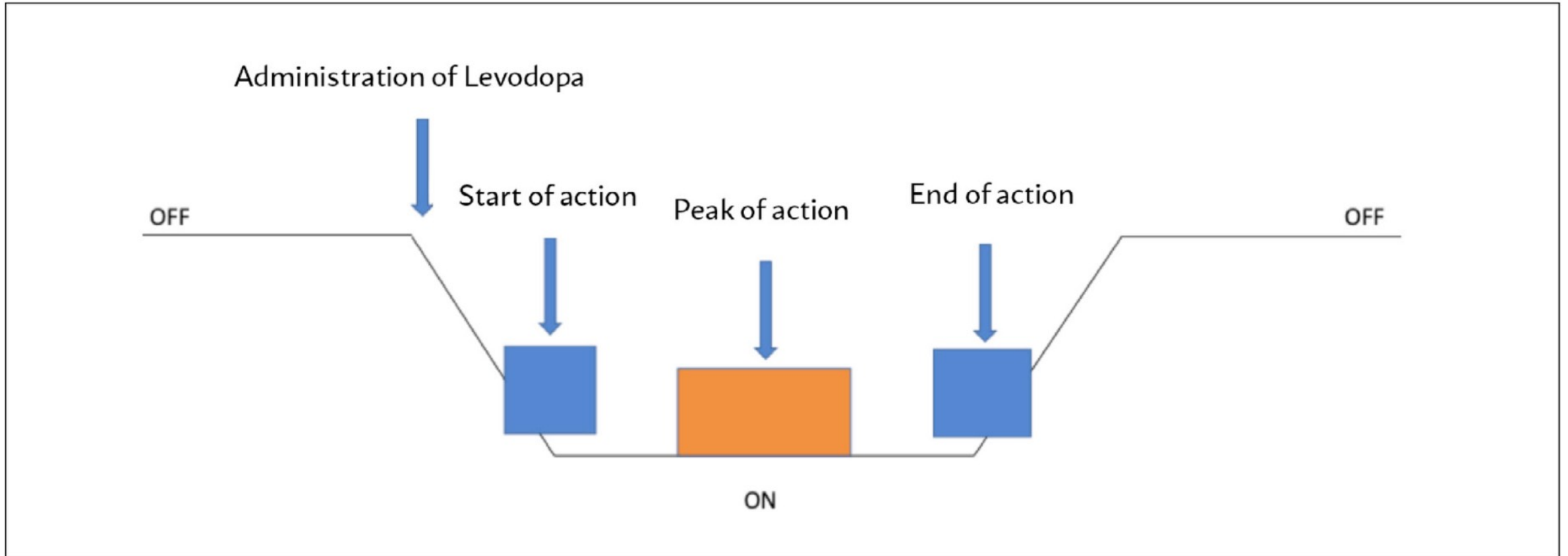
Outline

1. Treatment paradigms: the standard
2. OFF and ON definitions
3. Mechanisms for motor fluctuations with progression
4. New developments in treatment “On Demand”

Standard Dosing

- The standard model for Parkinson's disease medication management is scheduled doses of medications throughout the day
- Adherence to regular dose schedules leads to more consistent and predictable response throughout the day
- Schedules facilitate compliance and patient/doctor communication
- However, this may hold only for early disease

OFF and ON



Progression of disease

- With progression of disease, reliability of doses and ON time can begin to vary
- Dose intervals may increase, additional doses are taken as needed
- OFF states are defined as periods where medication dose effect is not as predicted
- OFF can consist of return of motor or nonmotor symptoms (i.e., anxiety, sweating, pain, etc.) at predictable or unpredictable times
- OFF episodes are experienced by nearly 60% of patients with PD within the first 4-6 years after diagnosis

ON/OFF Fluctuation with Progression

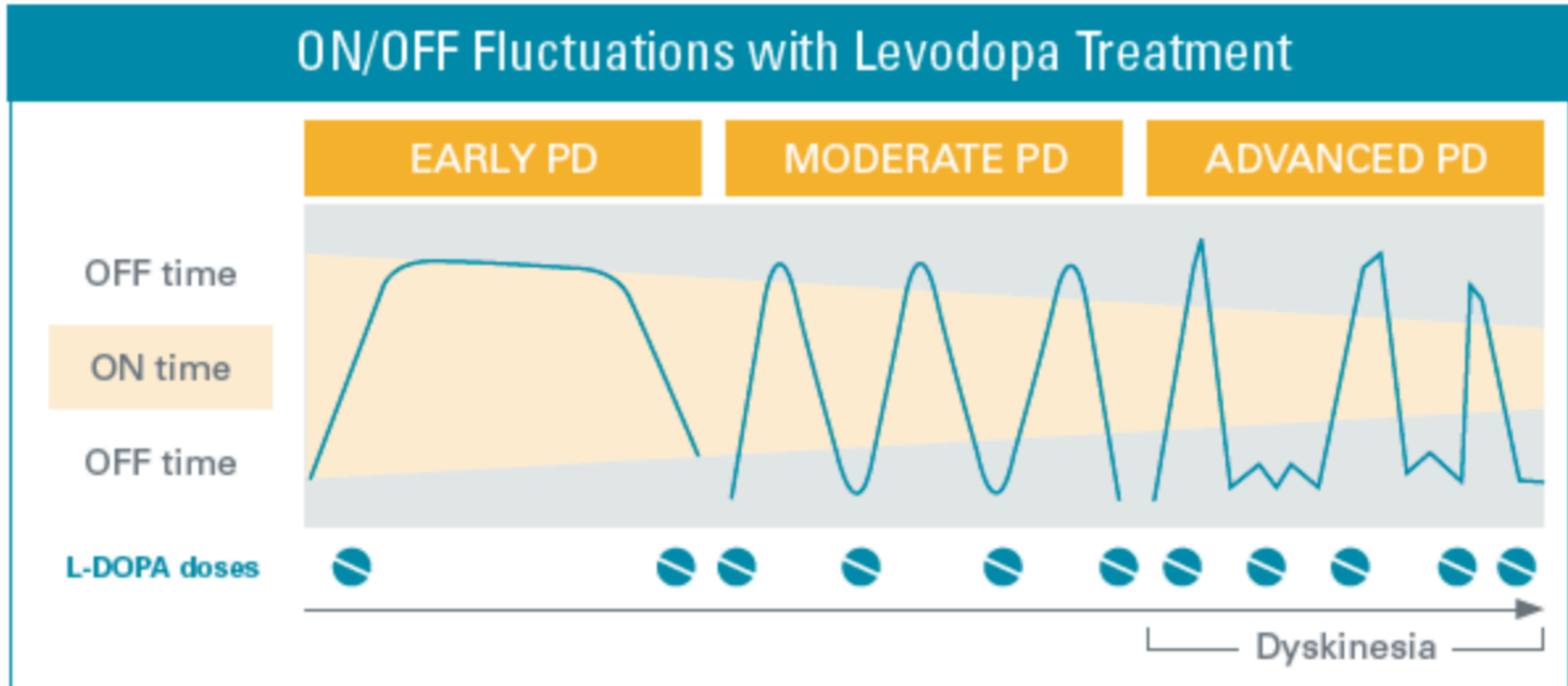
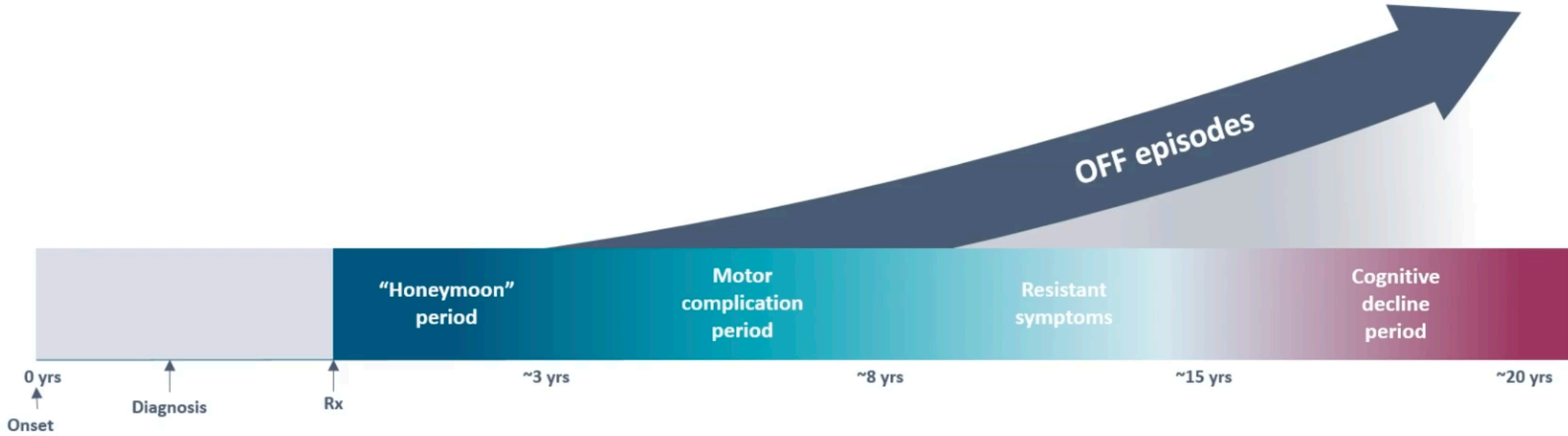


Image courtesy of Boston Scientific.

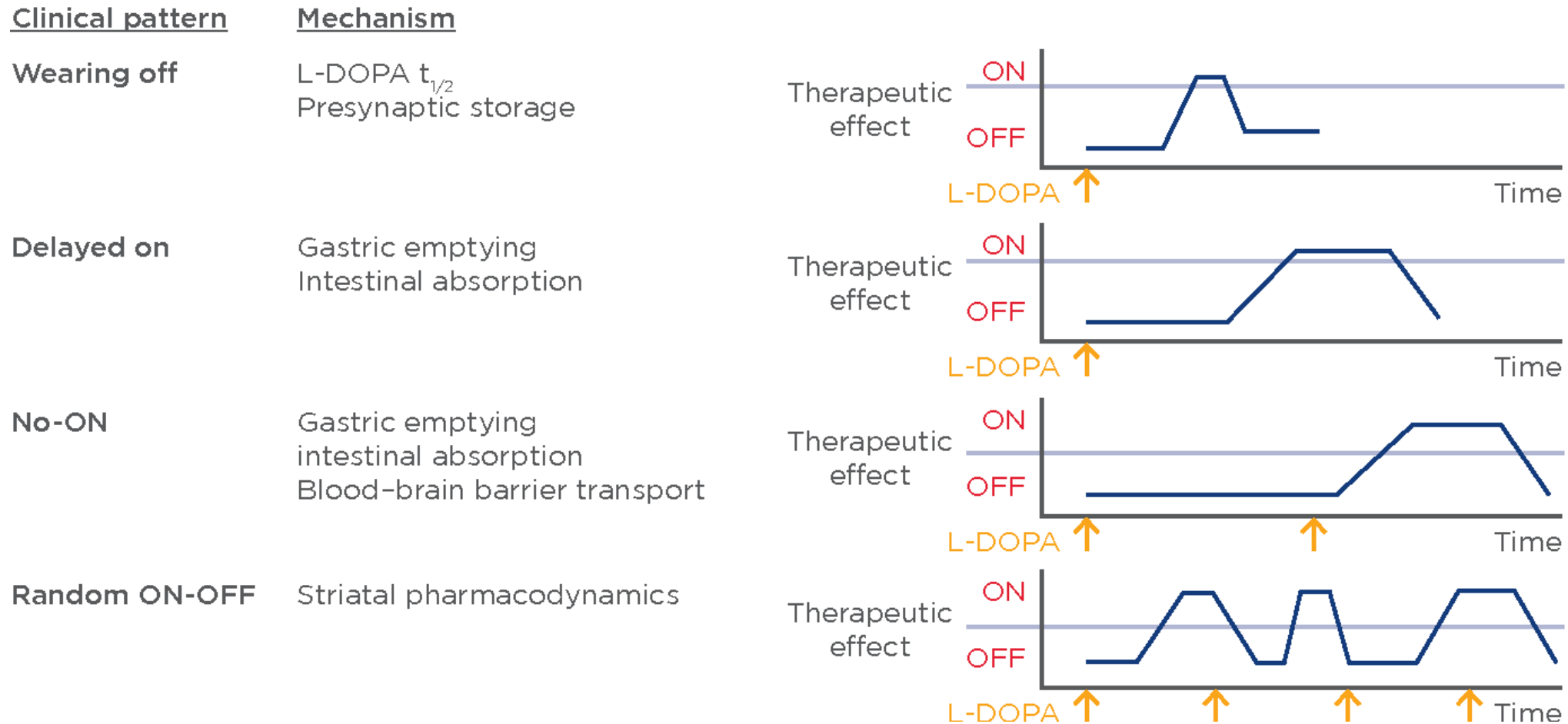
The Likelihood of OFF Episodes Occurring in Patients With PD Taking Levodopa* Increases Over Time¹⁻⁴



Various forms of ON/OFF

- Morning OFF
- Wearing OFF at the end of dose
- Delayed ON/Partial ON/No ON (Dose failure)
- Unpredictable OFF

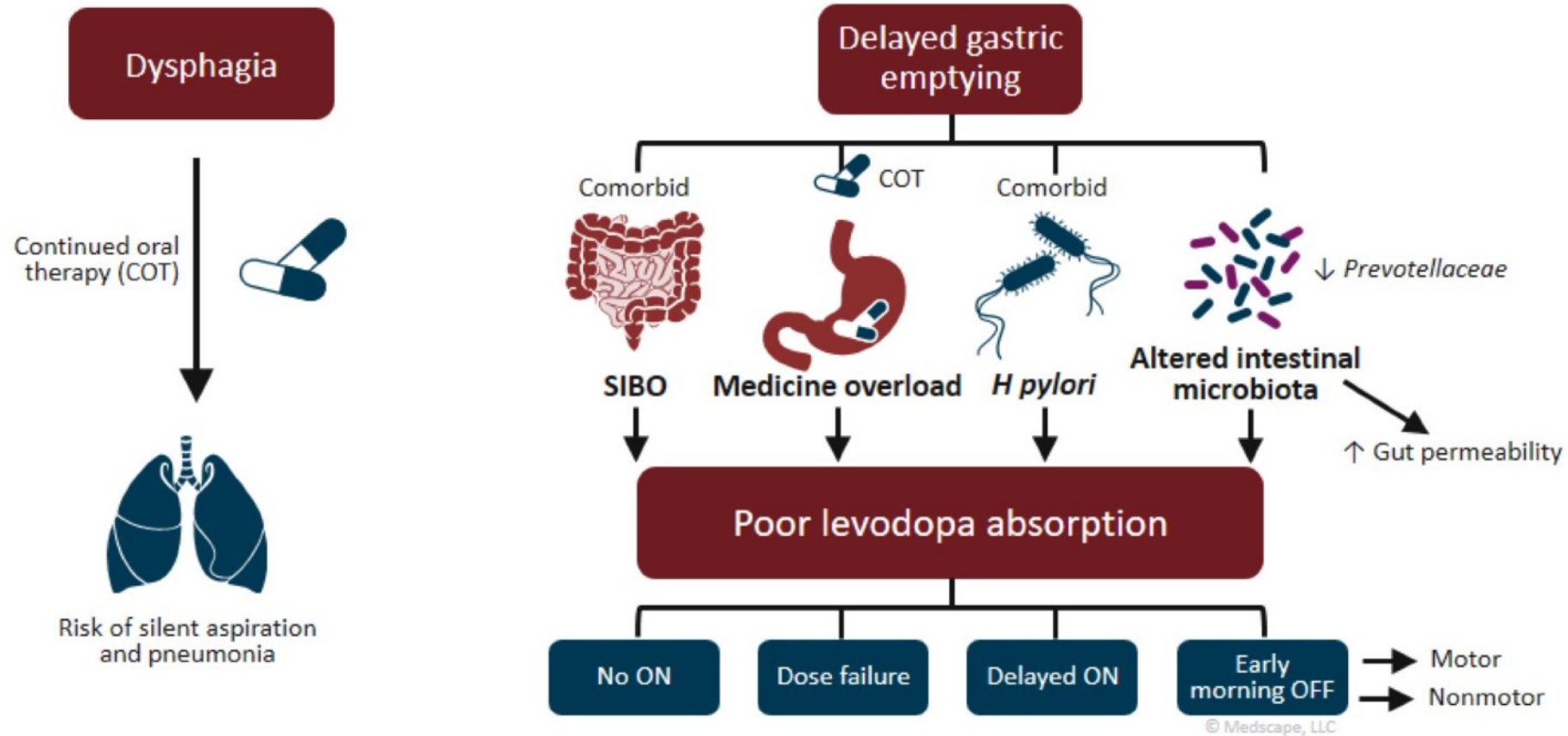
Forms of ON/OFF



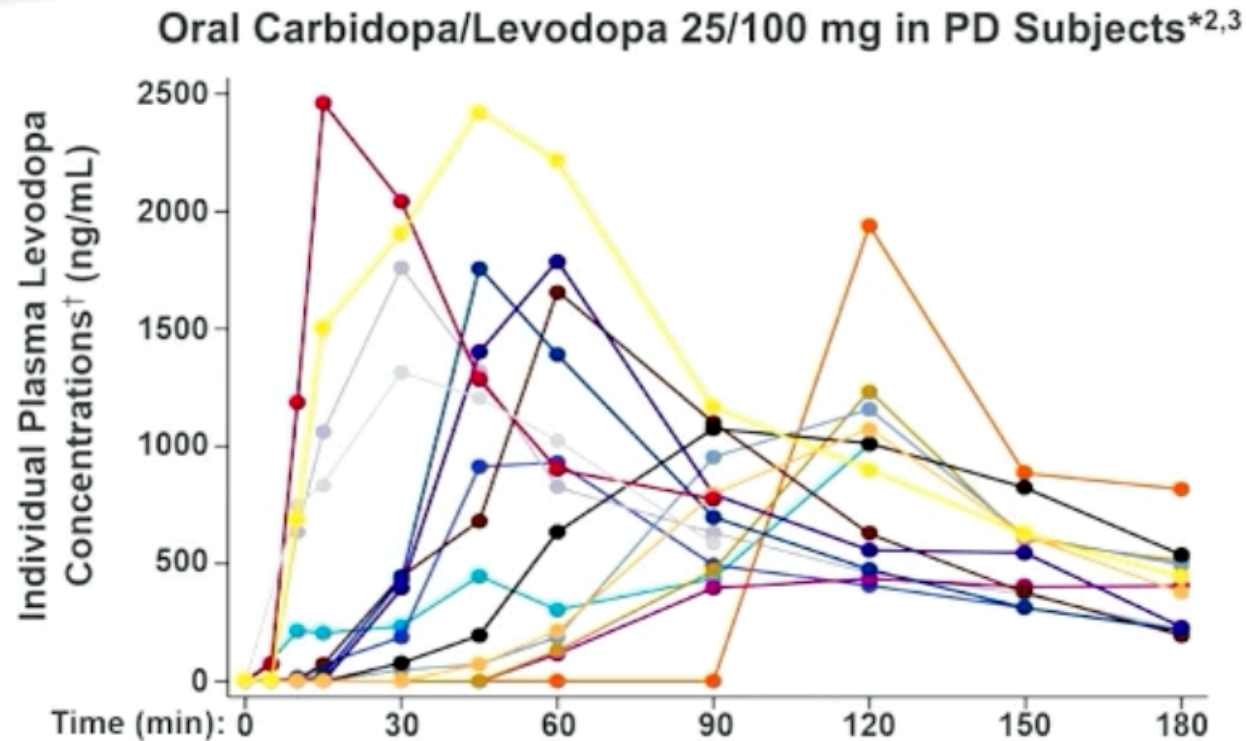
Causes for motor fluctuations

- Central causes
 - Progression of dopamine neuron degeneration
 - Inability to buffer shifts in levodopa due to periodic oral dosing
 - Changes in dopamine receptor sensitivity
- Peripheral causes
 - Gastric emptying delay
 - Erratic absorption in the intestine
 - Competition with amino acids

Delayed Onset and End-of-Dose Wearing Off



Variability in Absorption of Oral Carbidopa/Levodopa Contributes to the Return of PD Symptoms¹



Inter- and intra-
individual variability in
levodopa absorption
is largely due to
variation in
gastric emptying⁴

*No food at least 1 hour before and 1 hour after carbidopa/levodopa dose.

[†]Variable adjusted.

From Lipp MM, Batycky R, Moore J, Leinonen M, Freed MI. Preclinical and clinical assessment of inhaled levodopa for OFF episodes in Parkinson's disease. *Sci Transl Med.* 2016;8(360):360ra136. Reprinted with permission from AAAS.

1. LeWitt PA. *Mov Disord.* 2015;30(1):64-72. 2. Lipp MM et al. *Sci Transl Med.* 2016;8(360):360ra136. 3. Data on File. Acorda Therapeutics. 4. Nyholm D et al. *Clin Neuropharmacol.* 2002;25(2):89-96.

Gastroparesis is a common cause of OFF

- Delay of levodopa emptying from the stomach into the small intestine
- Leads to delayed time to ON and morning akinesia
- May explain dose failures and suboptimal-ON
- **Bypassing the gut may be important to treating OFF symptoms with progression in PD**

“On-Demand”

- On-demand refers to medications taken acutely for rescue of OFF periods
- Implies the need for a fast acting solution
- Ideally is not taken all the time as part of standard scheduled dosing
- Previously, options were limited in this space

Options for On-Demand Treatment

- Apokyn – subcutaneous apomorphine injection
- Liquid levodopa formulation
- Inbrija - inhaled levodopa
- Kynmobi – sublingual apomorphine

Apomorphine

- A fast acting dopamine agonist
- Potency has been shown to be comparable to L-dopa
- Not an opioid despite the name
- Due to hepatic metabolism, leads to poor oral bioavailability
- Is only available in subcutaneous injection or continuous infusion in Europe
- Recently a sublingual formulation was approved and is now available

Subcutaneous Apomorphine Injection: Apokyn

- An established medication for over 25 years
- A subcutaneous injection that can be self-administered
- Improved motor scores within 4-12 minutes in 95% of patients
- Duration of clinical effect ranges from 40-90 minutes
- Side effects include severe nausea/vomiting, orthostatic hypotension, dyskinesias

Apokyn: Use scenarios

- Sudden and unpredictable changes in symptoms
- Severe OFF periods not controlled by other medications
- Severe swallowing difficulties limiting oral medications

Apokyn

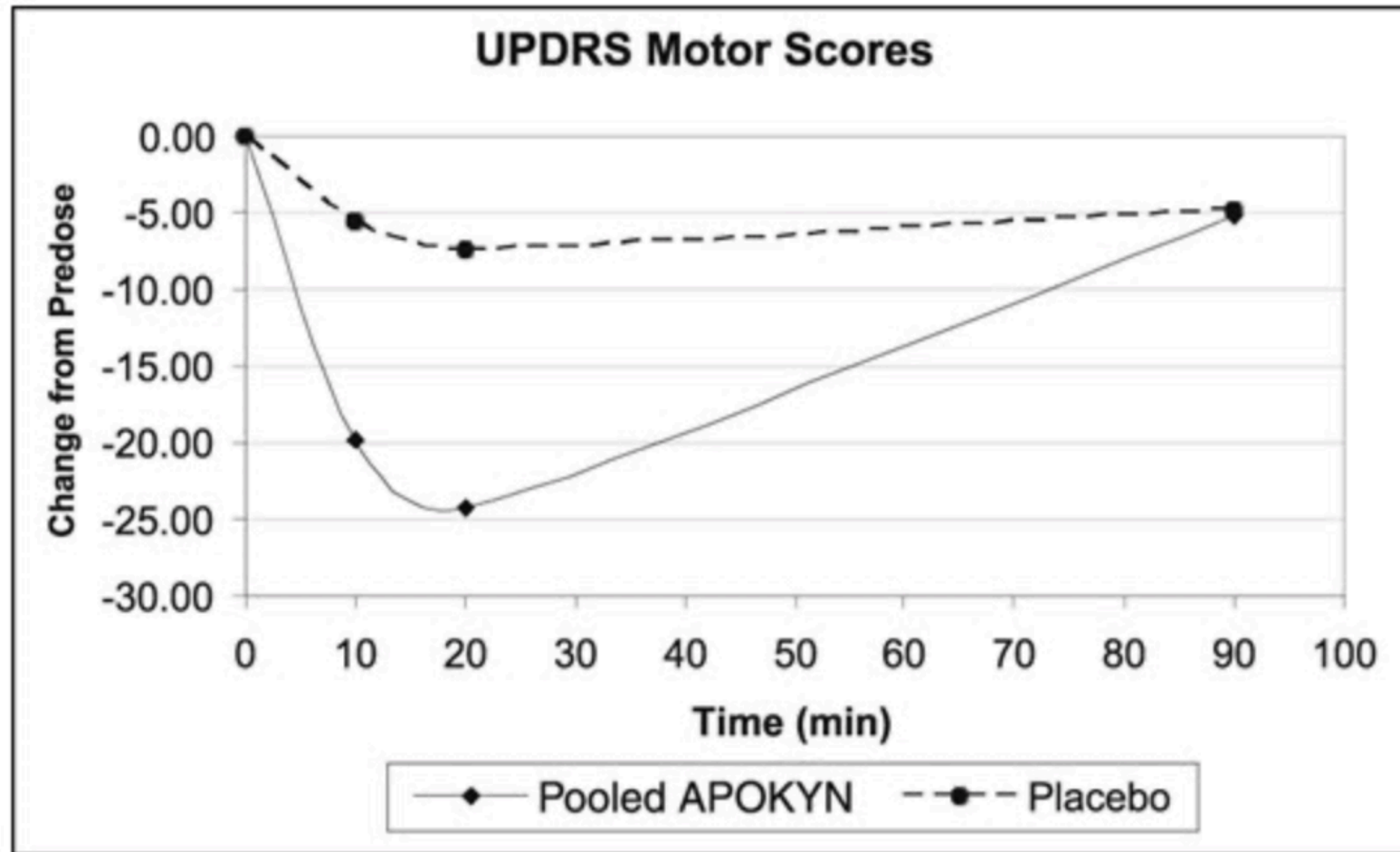
Very fine (29 gauge) needle, similar to that used by patients with diabetes who require insulin injections

Easy-to-use dose dial



Replaceable multi-dose, 3-mL cartridges
available through Specialty Pharmacy Providers

Apokyn onset is fast and of moderate duration



Apokyn: Side effects

- Nausea is a major side effect
- Pretreatment with Tigan (Trimethobenzamide 300 mg three times a day) is recommended prior to starting
- Orthostatic hypotension can be seen, so first dose is best monitored in a doctor's office
- Other side effects of dopamine agonists can occur including hallucinations, sedation, compulsions or dyskinesias

Disincentives to Apokyn adoption

- Despite efficacy, Apokyn is not used as much as it could be
- Injections may be daunting
- Akinetic patients have difficulty performing injection
- Use of the Apokyn pen has multiple instruction steps
- Side effects may be limiting

Liquid levodopa

- Levodopa tablets may be dissolved in water stabilized with vitamin C
- A homegrown method for OFF rescue
- Cheap and effective
- Works faster than oral tablets, solution passes faster through GI tract
- **Formula:** 10 tablets of 25/100 or 10/100 mg levodopa with 2 g of ascorbic acid powder in 1 Liter water (1 mg/mL concentration)
- May require more frequent dosing to achieve control

Inbrija

- Inhaled levodopa
- Used to treat OFF time in an on-demand fashion
- Each dose consists of 2 42-mg capsules
- No more than 5 doses in one day
- Approved in 2018 available since last year



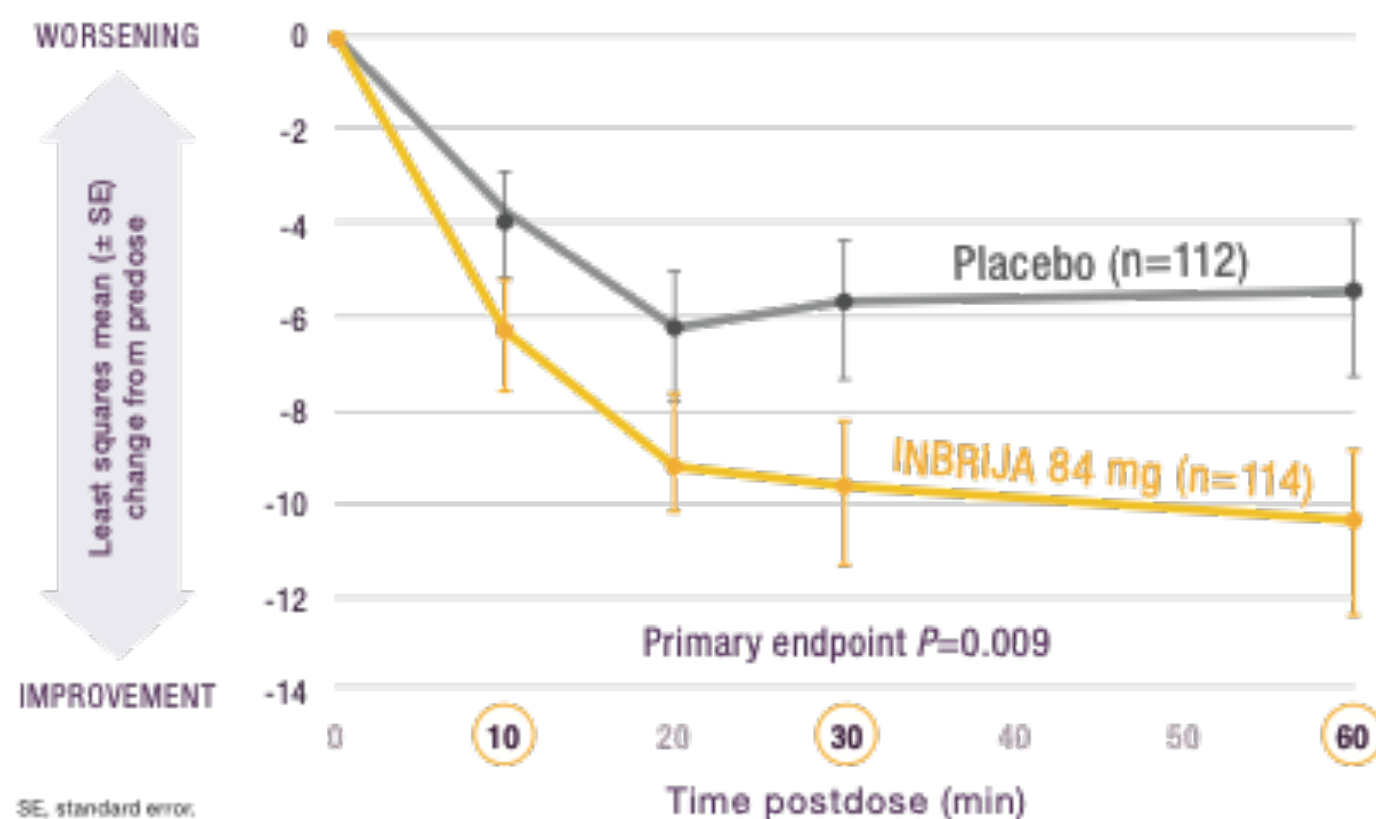
Inbrija

- May take effect in 10 minutes and last up to 60 minutes
- Does not replace standard oral dosing of Sinemet which should be continued
- Scheduled doses should still be taken
- Best for rescue of OFF or delayed ON

SPAN-PD RESULTS:

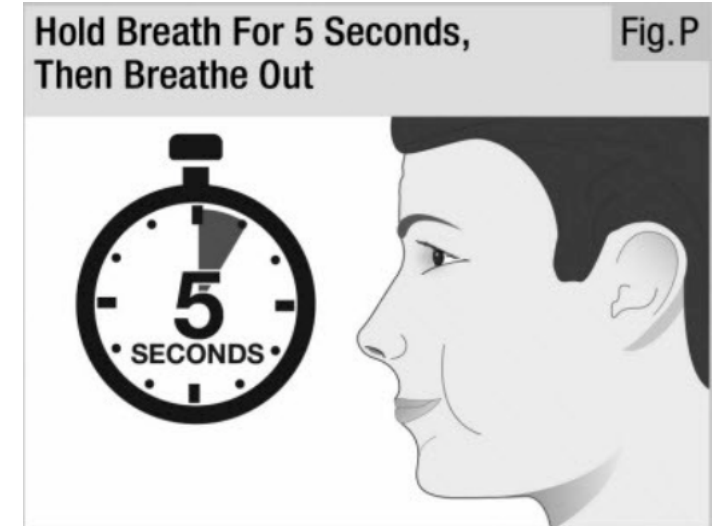
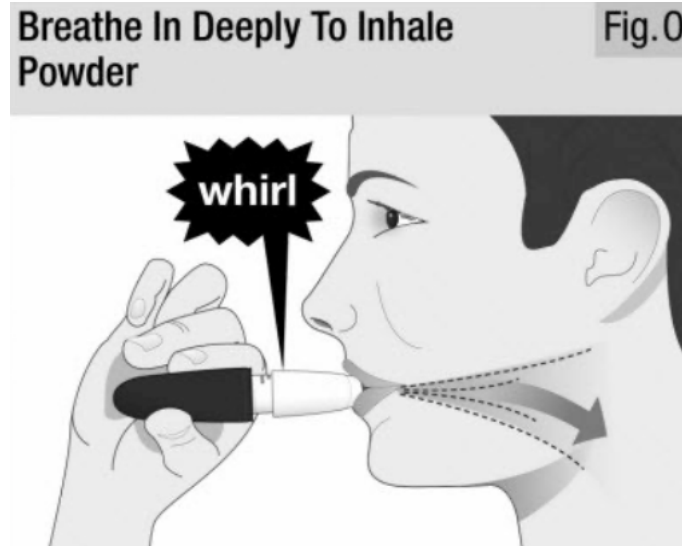
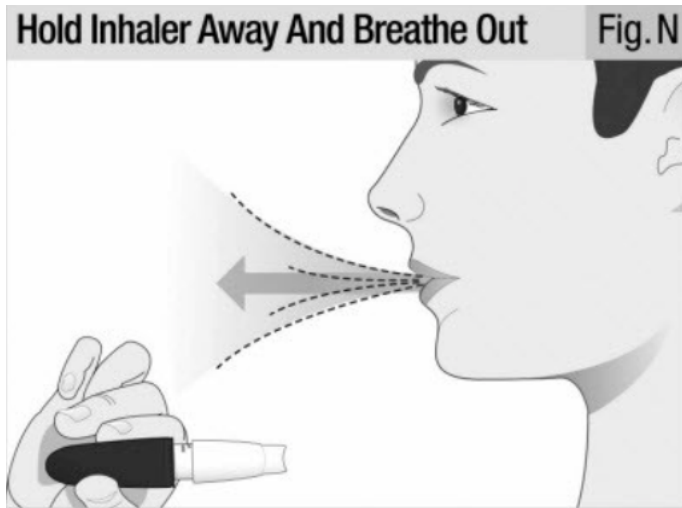
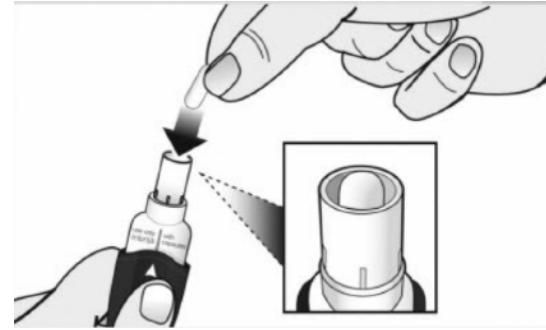
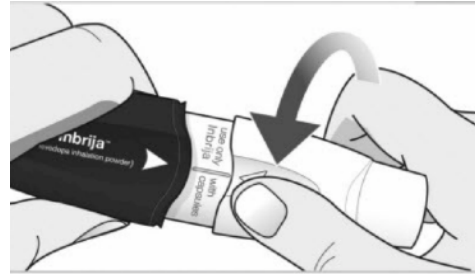
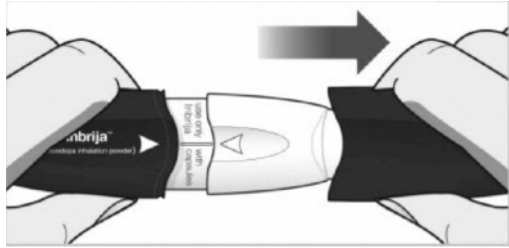
INBRIJA SIGNIFICANTLY IMPROVES MOTOR FUNCTION IN PATIENTS WITH PARKINSON'S EXPERIENCING OFF PERIODS

UPDRS Part III score change from 0-60 minutes postdose at week 12



SE, standard error.

Inbrija instructions



Inbrija

- Not recommended in patients with asthma, COPD or or chronic lung disease due to bronchospasm
- Most common adverse reactions were cough, nausea or discolored sputum
- May cause dyskinesias as well similar to levodopa but were not found to be troublesome in studies

Kynmobi

KYNMOBI™
(apomorphine HCl) sublingual film
10 mg • 15 mg • 20 mg • 25 mg • 30 mg

**KYNMOBI™ (apomorphine HCl) Sublingual Film:
A Unique Formulation of Apomorphine**



10mg 15mg 20mg 25mg 30mg

KYNMOBI (apomorphine hydrochloride) sublingual film

Kynmobi

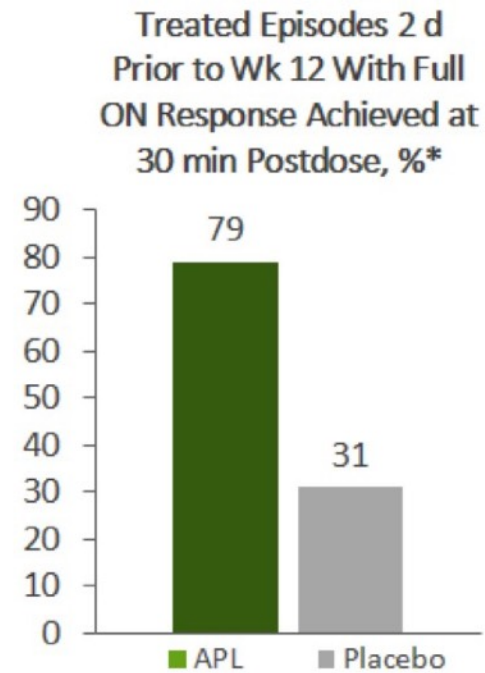
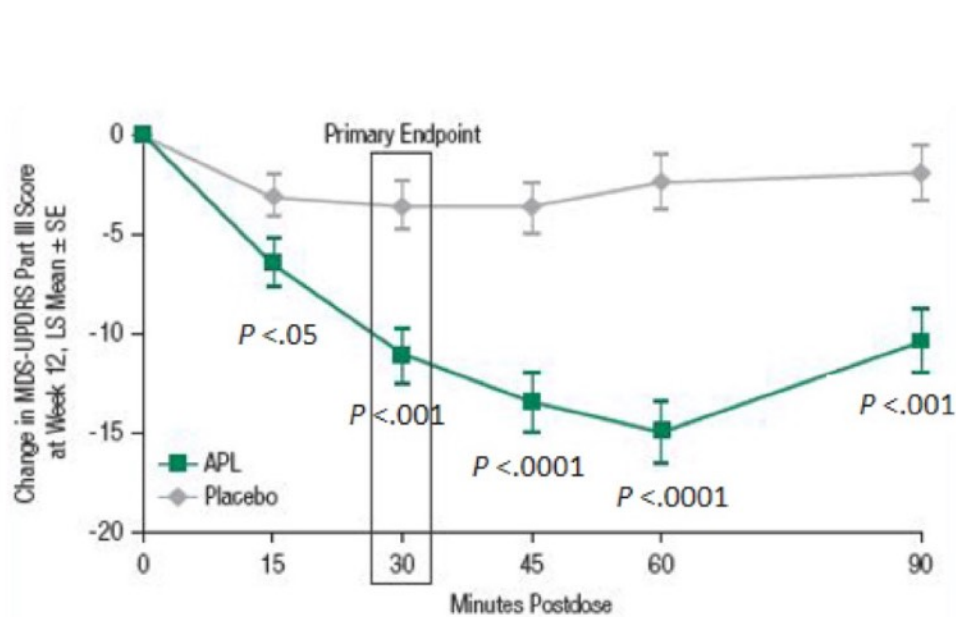
- A sublingual film indicated for the acute, intermittent treatment of OFF episodes in PD
- Approved with first samples and prescriptions starting September 2020
- Contraindicated in patients using antiemetics of the 5HT3 antagonist class (Zofran, Granisetron)

Kynmobi

- Sublingual formulation uses a thin film delivery system that dissolves in saliva for quick absorption
- Bypasses liver metabolism
- No more than 5 doses a day, each dose > 2 hours
- May range from 10-30 mg in dose
- Clinical improvement observed at 15 minutes and lasting up to 90 minutes

APO Sublingual Film for OFF Episodes

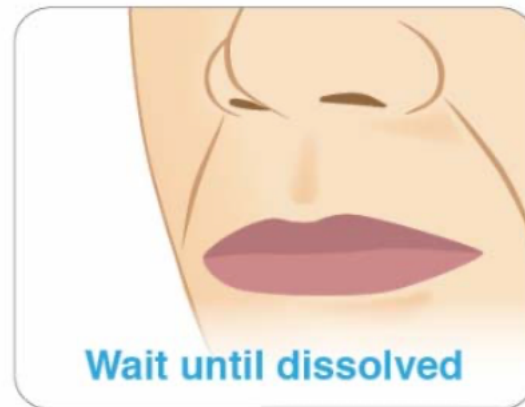
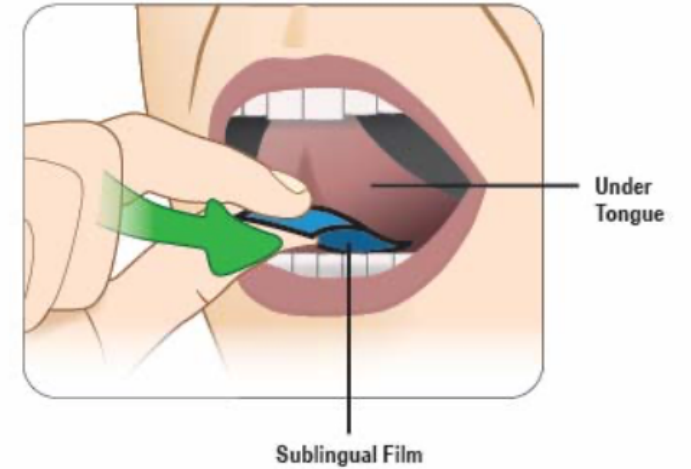
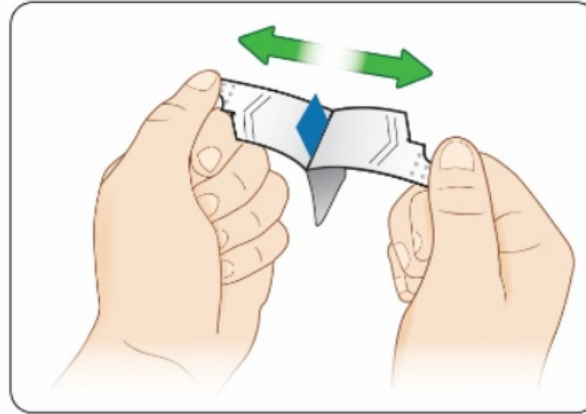
Results



- Most AEs generally mild and reversible upon treatment discontinuation
- Most common AEs: Nausea, somnolence, dizziness, oral mucosal erythema

*Based on home dosing diary (modified ITT population)
Factor S, et al. ICPDMS 2018. P 247.

Kynmobi Instructions



Kynmobi: Antiemetic pretreatment

- Nausea and vomiting are a common side effect of Apomorphine
- Similar to Apokyn, pretreatment with an antinausea medication is recommended
- Trimethobenzamide 300 mg (Tigan) three times a day is recommended prior to starting Kynmobi
- Nausea and vomiting may resolve with time

Kynmobi: Side effects

- Nausea/vomiting
- Somnolence
- Orthostatic hypotension or fainting
- Oral soft tissue swelling or mucosal irritation
- Hallucinations/impulse control disorders

Advantages of on-demand versus routine dose adjustments

- Less overall medication load
- Bypassing gastroparesis and oral dose problems
- Less side effects potentially (dyskinesias, nausea)
- More vigilance to symptoms and medication compliance
- Personalized dosing

Costs

- Apokyn – \$5752 for 15 mL – Medicare co-pay \$89-398
- Inbrija – \$1000. mm for supply of 60 capsules - Medicare co-pay \$4-2185
- Kynmobi – \$8 for supply of 10 films

Pros and Cons of rescue therapies

Therapy	Pros	Cons
Apokyn	Effective and established	Invasive Cost Side effects
Inbrija	Convenient Minimal side effects	Cost
Kynmobi	Convenient	Side effects including nausea Cost
Liquid levodopa	Cheap Titratable	Inconvenient to make

Available and Investigational Nonoral Therapies

Subcutaneous	Transdermal	Intrajejunal Infusion	Buccal	Inhaled powder
Apomorphine pen ^[a]	Rotigotine patch ^[d]	Carbidopa-levodopa enteral suspension ^[e]	Apomorphine sublingual film* ^[f]	Levodopa-carbidopa ^[h]
Apomorphine pump* ^[b]			Zydis selegiline ^[g]	
Carbidopa-levodopa pump* ^[c]				

*Not FDA approved.

a. Apokyn[®] PI. 2017; b. Katzenschlager R, et al. *Lancet Neurol.* 2018;17:749-759; c. ClinicalTrials.gov. NCT02726386; d. Neupro PI. 2012; e. Duopa[™] PI. 2016; f. Pahwa R, et al. *Mov Disord.* 2018; 33 (suppl 2); g. Zelepar PI. 2014; h. Inbrija[™] PI. 2018.

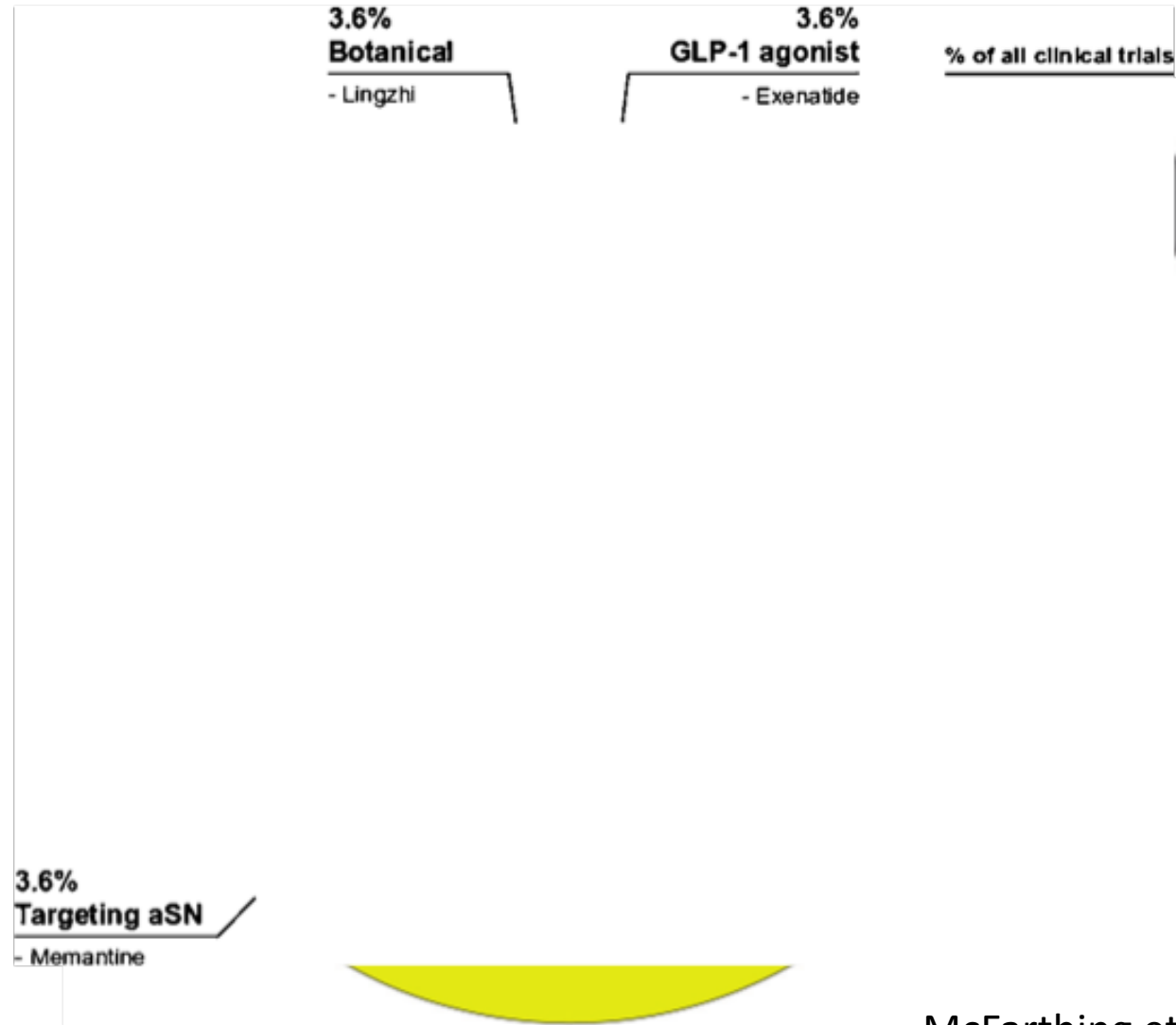
Summary

- A variety of old and new options exist to address OFF symptoms in an acute on-demand manner
- New formulations bypass the digestive system to deliver medications to the nervous system
- Side effects and costs may limit the utility of these agents for individual patients

Other new available treatments

- August 2019: Nourianz/Istradefylline – Adenosine Receptor Antagonist
- August 2020: Ongentys/Opicapone – COMT inhibitor once a day
- Both are adjunctive medications to levodopa to prolong ON time and reduce OFF time

Ongoing Phase 3 clinical trials



McFarthing et al., 2020

Ongoing total clinical trials for PD

