UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

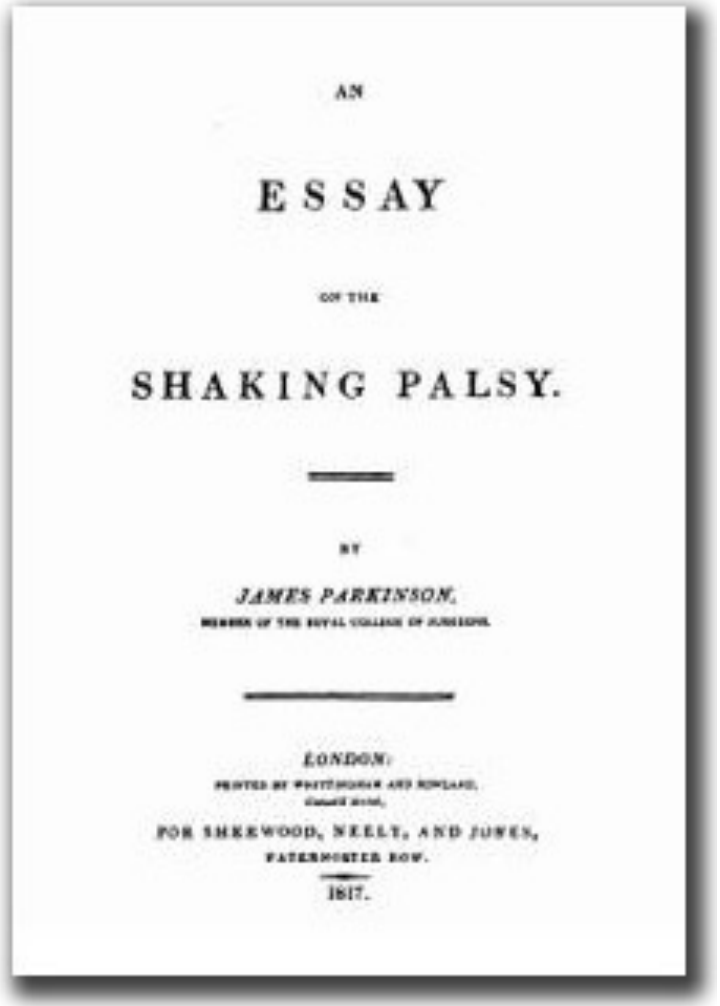
Present and Future Pharmacological therapies in Parkinson's Disease

2024 PASWFL Symposium
April 4, 2024

Henry Moore, MD

Associate Professor of Neurology – University of Miami – Miller School of Medicine
Parkinson Disease and Movement Disorders Center – Parkinson Foundation – Center of Excellence
Director of Movement Disorders for Palm Beach County

James Parkinson and “An Essay on the Shaking Palsy”



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Cannon Row,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

James Parkinson
(1755-1828)

History of levodopa: From James Parkinson to George Cotzias

George Cotzias
(1918-1977)

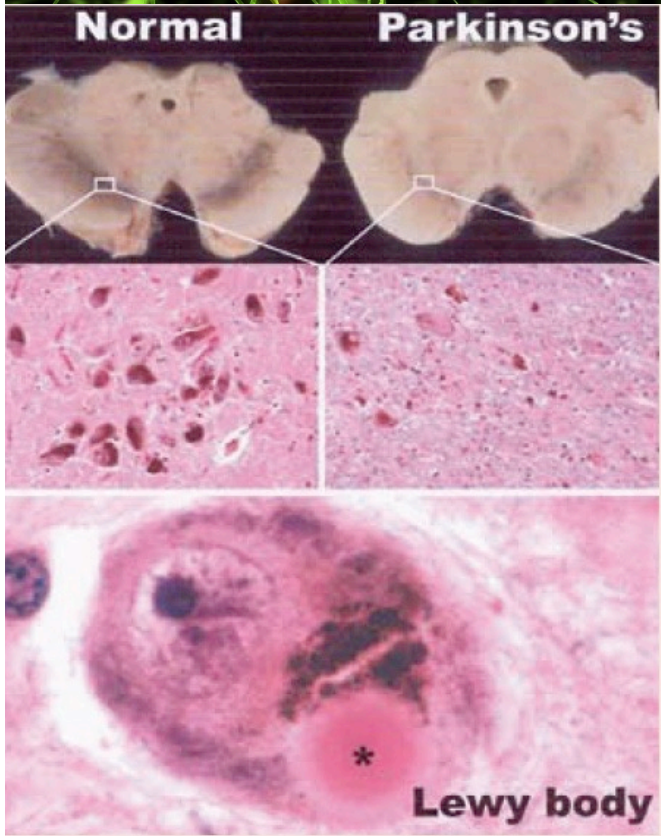
. . . It took 150 years since James Parkinson description in 1817 of the illness bearing his name until the development of effective therapy for this disorder, high dose levodopa by George Cotzias in 1967…

What is PD?

-Parkinson's disease is a slowly progressive, neurodegenerative disorder that occurs when the brain cells (neurons) in an area of the brain called substantia nigra die or became impaired.

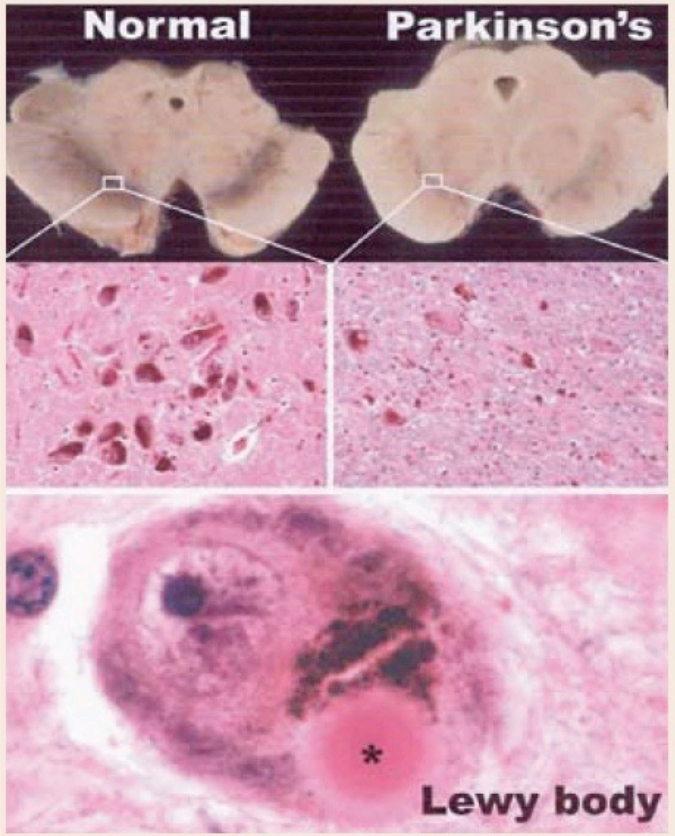
-The neurons more impaired are the ones that produce a vital substance called dopamine.

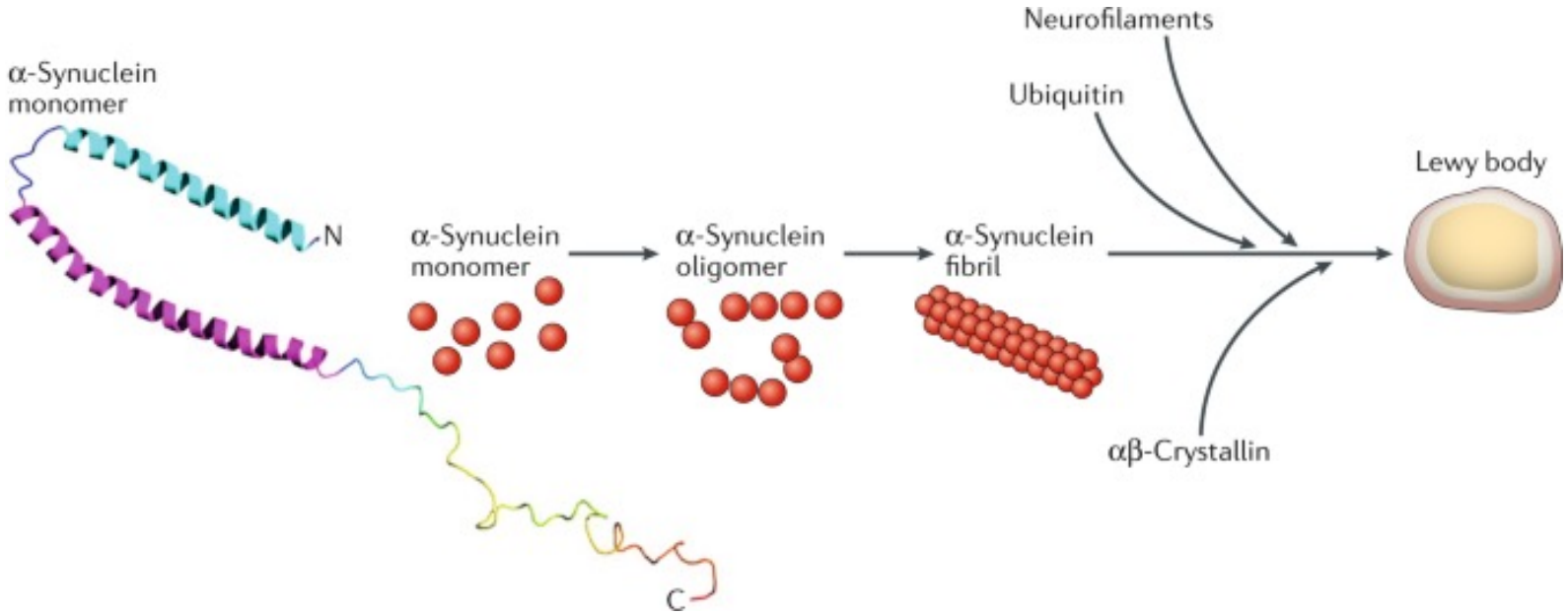
-Dopamine is a chemical messenger in the brain, and its presence in the brain is very important in the generation of movement.



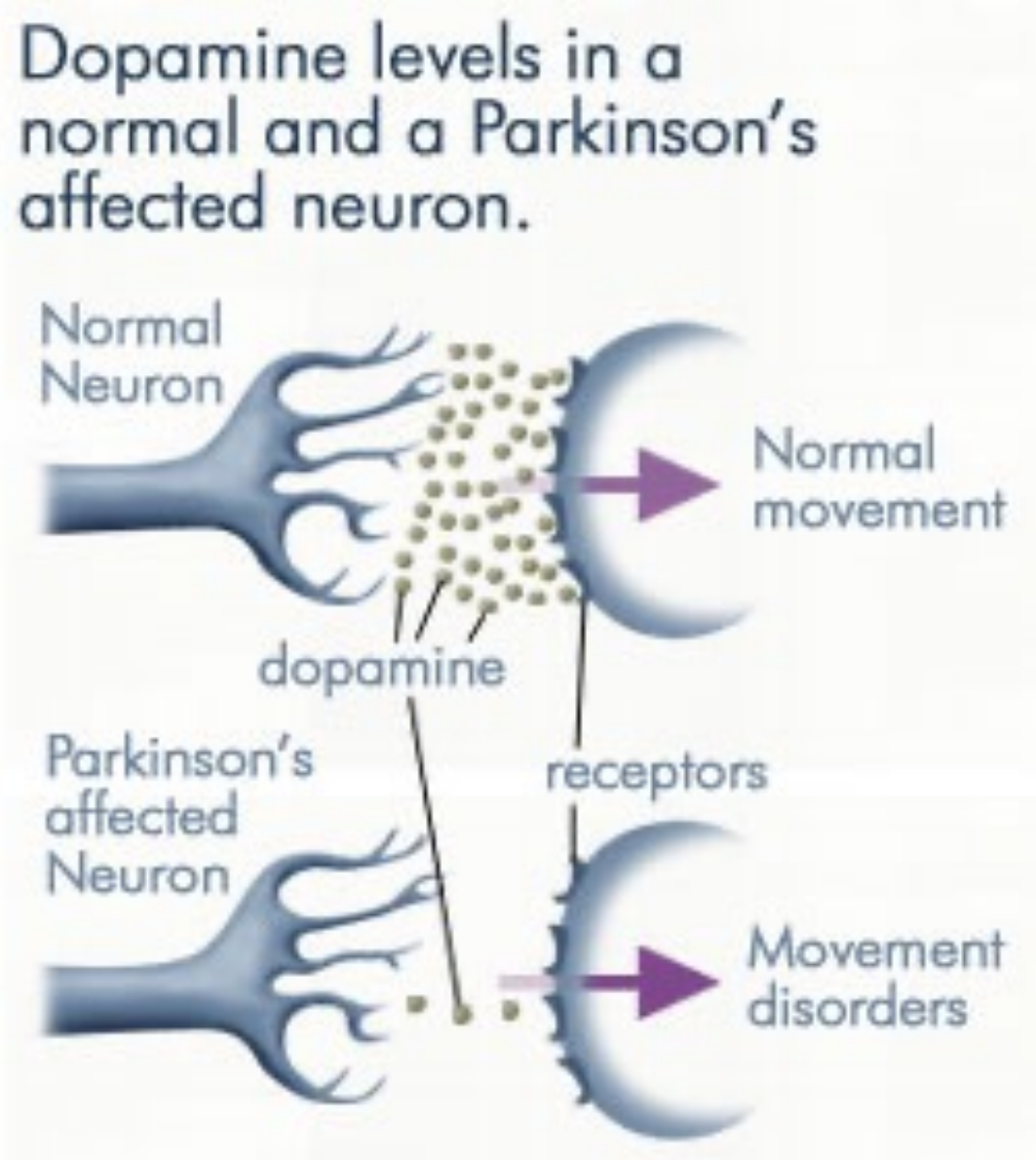
Lewy Bodies: Aggregated alpha synuclein accumulation in neurons

Figure 1. Appearance of the substantia nigra in a normal midbrain and in the midbrain of a patient with Parkinson disease: *In the normal midbrain, the substantia nigra is darkly pigmented. In idiopathic Parkinson disease, marked pallor is due to degeneration and loss of dopaminergic neurons. Some of the surviving neurons contain characteristic eosinophilic Lewy body inclusions.*





Dopamine: the generator of movement



Slowness
Rigidity
Tremor at rest
Gait disorder

Cardinal features of parkinsonism

- **EARLY FEATURES**
  - Bradykinesia / Hypokinesia / Akinesia
  - Rigidity (Cogwheel)
  - Tremor at rest (4-6Hz)

- **LATE FEATURES** (Most of them intractable)
  - Freezing of gait
  - Loss of postural reflexes
  - Abnormal postures (neck, trunk, limbs)

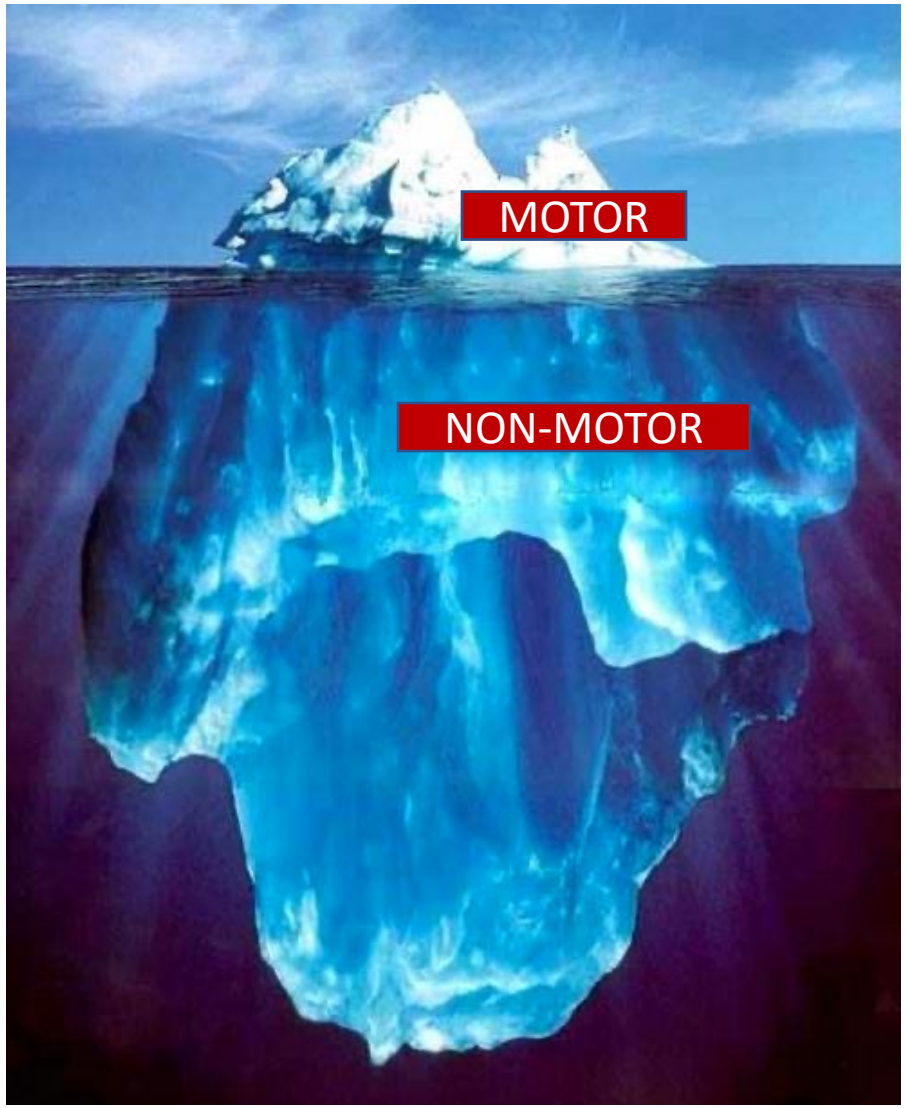
Cardinal features of parkinsonism

- **EARLY FEATURES**
  - Bradykinesia / Hypokinesia / Akinesia
  - Rigidity (Cogwheel)
  - Tremor at rest (4-6Hz)

- **LATE FEATURES** (Most of them intractable)
  - Freezing of gait
  - Loss of postural reflexes
  - Abnormal postures (neck, trunk, limbs)

FALLS

Motor symptoms: Just the tip of the iceberg



Depression, anxiety, panic attacks, apathy, fatigue

Mental slowness, memory problems, inability to multitask

Pain, tingling, numbness, poor sense of smell

Dizziness upon standing, abnormal sweating, nasal discharge, urinary urgency, constipation, seborrhea

Insomnia, fragmented sleep, diurnal sleepiness, vivid dreams, sleep talking, sleep fighting, restless legs, sleep apnea

New diagnosis of PD – Treatment Options

Individualized treatment

OPTION 1:
No treatment

OPTION 2:
Clinical trials participation

OPTION 3:
Symptomatic treatment

A. Low potency: amantadine, rasagiline, selegiline, ropirinole, pramipexole, rotigotine patches
B. High potency: CARBIDOPA/LEVODOPA
   Best and most potent medication for PD motor symptoms (developed in the 1960s)

Slowing down PD progression

At present, there is no known treatment to slow down PD.

FAILURES

- Neuroimmunophilin A
- Riluzole
- Liatermin (IP GDNF)
- AAV2 – Neurturin
- Levodopa
- Coenzyme Q10
- Creatine
- Pramipexole
- Pioglitazone
- Isradipine
- Inosine
- Nilotinib
- N-acethylcysteine
- Nicotine
- Statins
- Caffeine
- GDNF (Glial derived neurotrophic factor)

IN DOUBT

- Selegiline
- Rasagiline
- Anti-inflammatory medications
  -AZD3241 (Inhibidor MPO)
  -Sgramostin (GMCSF recombinant)
  -ViNeuro
  -Transplant IV of autologous stem cells from adipose stroma
  -MCC950: NLP|RP3 inflammasome inhibitor
- Exercise

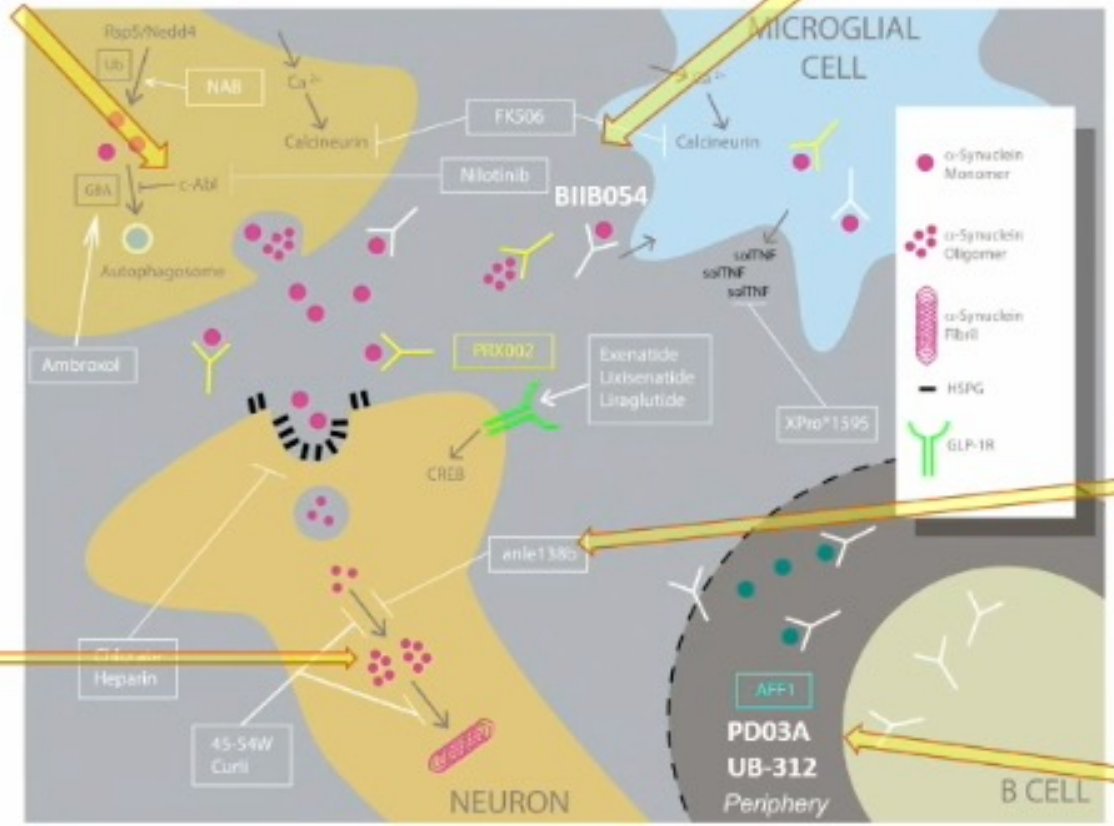
UNDER INVESTIGATION

- α-Sinuclein target
- Agonists of GLP-1 receptor: Exenatide (NLY01), liraglutide, lixisenatide, semaglutide)
- Glutathione
- N-acetylcysteine
- GM1 ganglioside
- Sagramostim
- Therapy targeting genes involved in genetic PD:
  - LRKK2
  - GBA

Alpha Synuclein target

Inducing autophagic degradation of α-synuclein aggregate (c-ABL1 inhibitors)

- **Vodobatinib,K0706** (PROSEEK, NCT03655236), **on-going Phase 2**
- **Radotinib** (NCT04691661), **on-going Phase 2**
- **ikt-148009** (NCT04350177), **on-going Phase 1**



Adapted from Brundin et al., MDJ, 2015

Passive immunization

- **BIIB054, Cinpanemab** (**Phase 2 completed**) vs nonmonomeric (SPARK)
- **PRX002, Prazinesumab** (**Phase 2 completed/Phase 2 on-going**) vs monomeric (PASADENA)
- **MEDI1341** (NCT04449484), **Phase 1 just concluded in 2022**, vs aggregated
- **Lu AF82422** (NCT03611569): **Phase 1, concluded in December 2021** vs aggregated and/or C-terminal truncated aSyn
- **UCB7853** (NCT04651153), **Phase 1 on-going**

Inhibition of α-synuclein misfolding

- **UCB0599** (ORCHESTRA, NCT04658186), concluded Phase 1- on going **Phase 2**

Inhibition of α-synuclein aggregation (stabilizing small molecule blockers)

- **Anle138b** (NCT04685265), on-going **Phase 1, target oligomeric forms**

Active immunization

- **PD03A**, completed Phase 1
- **UB-312,** completed, **Phase 1**

Symptomatic treatment for PD

Carbidopa / levodopa: (Sinemet ®) CD/LD, CD/LD extended release ER, CD/LD / entacapone (stalevo®), CD/LD ER (Rytary®), CD/LD enteral suspension (duopa®), CD/LD ODT (parcopa®), CD/LD inhaler (Inbrija®)

Dopamine Agonists

- Ergots: Bromocriptine (parlodel®), pergolide, cabergoline (dostinex®)
- Non-ergots: Pramipexole (mirapex ®), pramipexole ER, ropirinole (requip ®), ropirinole XL, rotigitine patch (neupro patch®), apomorhine SQ (apokyn®), apomorhine SL film (Kynmobi®)

Adenosine 2A Receptor Antagonists: Istradefylline (Nourianz®)

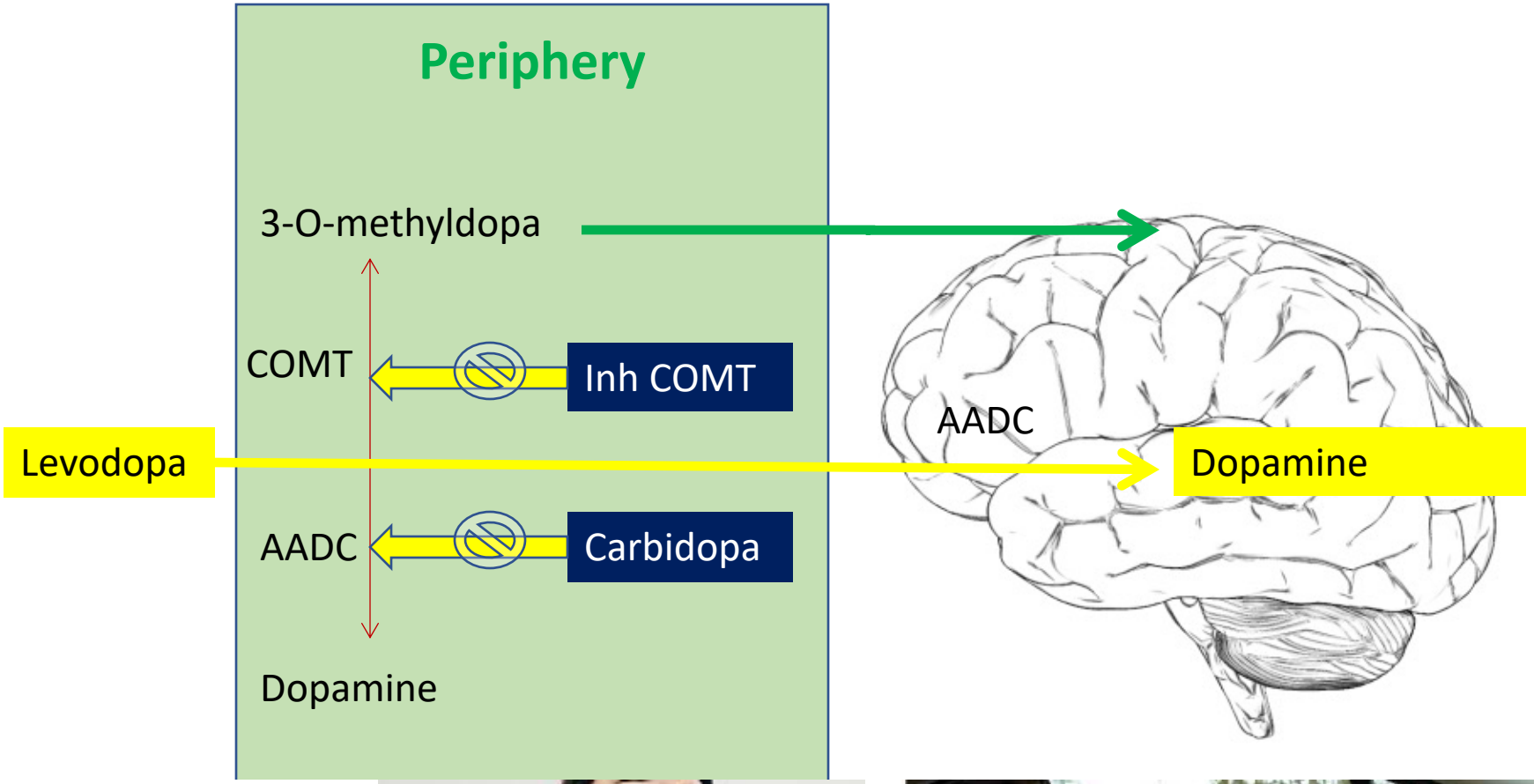
COMT inhibitors: Tolcapone (tazmar®), Entacapone (comtan®), Opicapone (Ongentys®)

MAO-B inhibitors: Selegiline (eldepryl®), selegiline ODT (Zelapar®), rasagiline (azilect®), Safnamide (Xadago®)

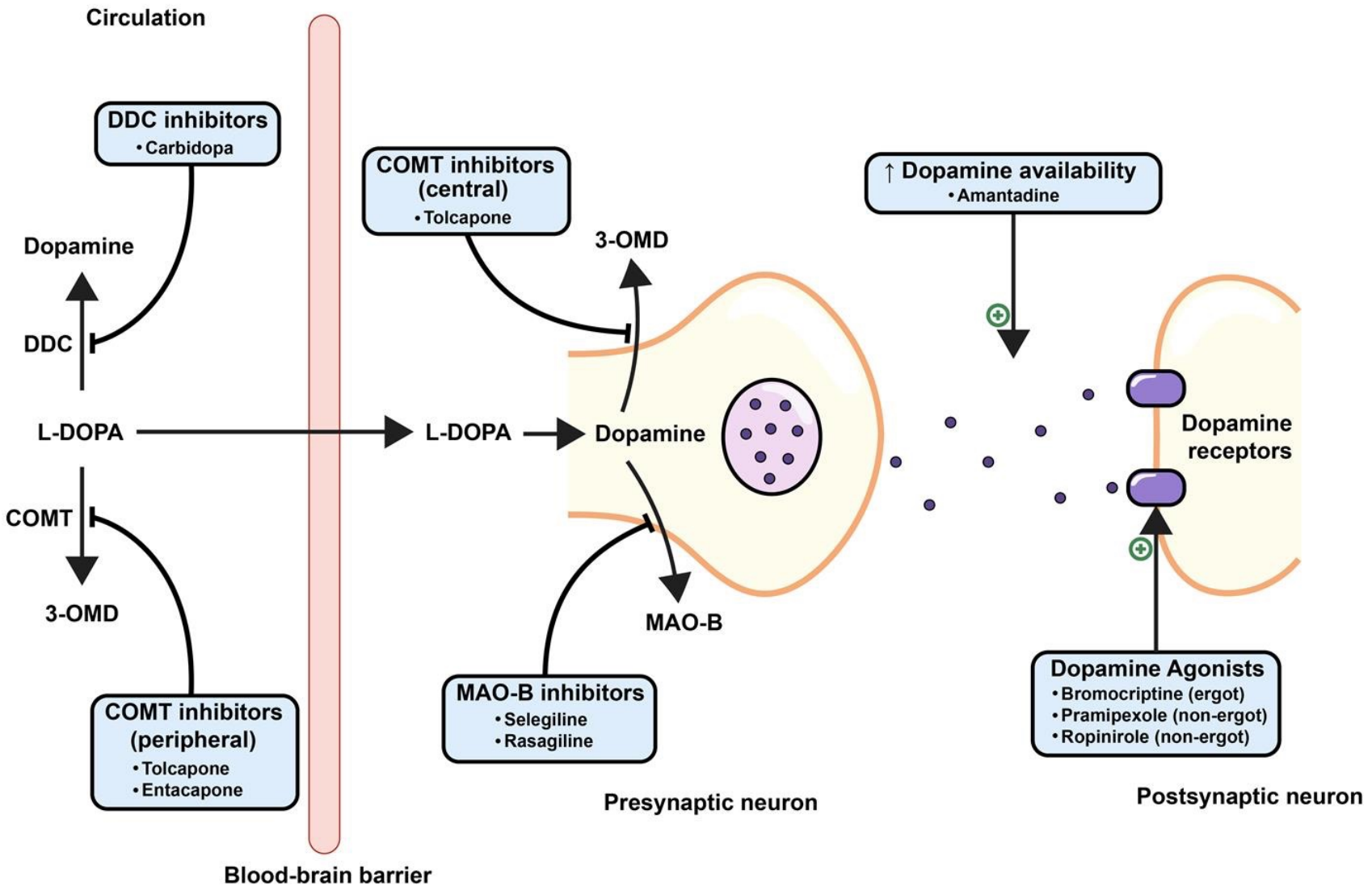
NMDA receptor antagonists: Amantadine (symmetrel®),Amantadine ER (Gocovri®), rimantadine (flumadine®)

Anticholinergics: Trihexyphenidyl, biperiden, benztropine

Levodopa


Periphery
3-O-methyldopa
COMT
Inh COMT
Levodopa
AADC
Carbidopa
Dopamine
AADC
Dopamine

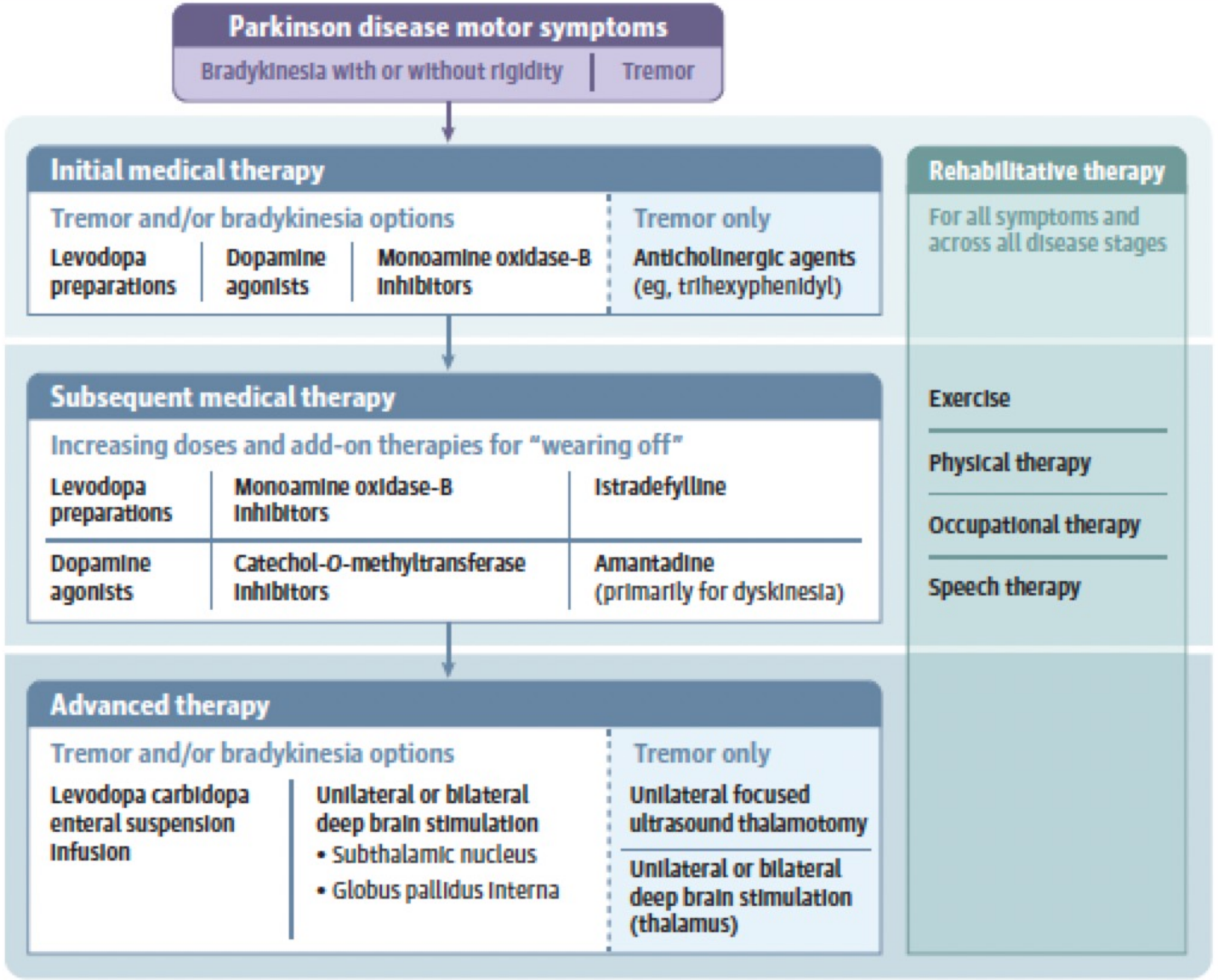
Mechanism of action of PD medications



Connolly and Lang, JAMA. 2014;311(16): 1670-1683

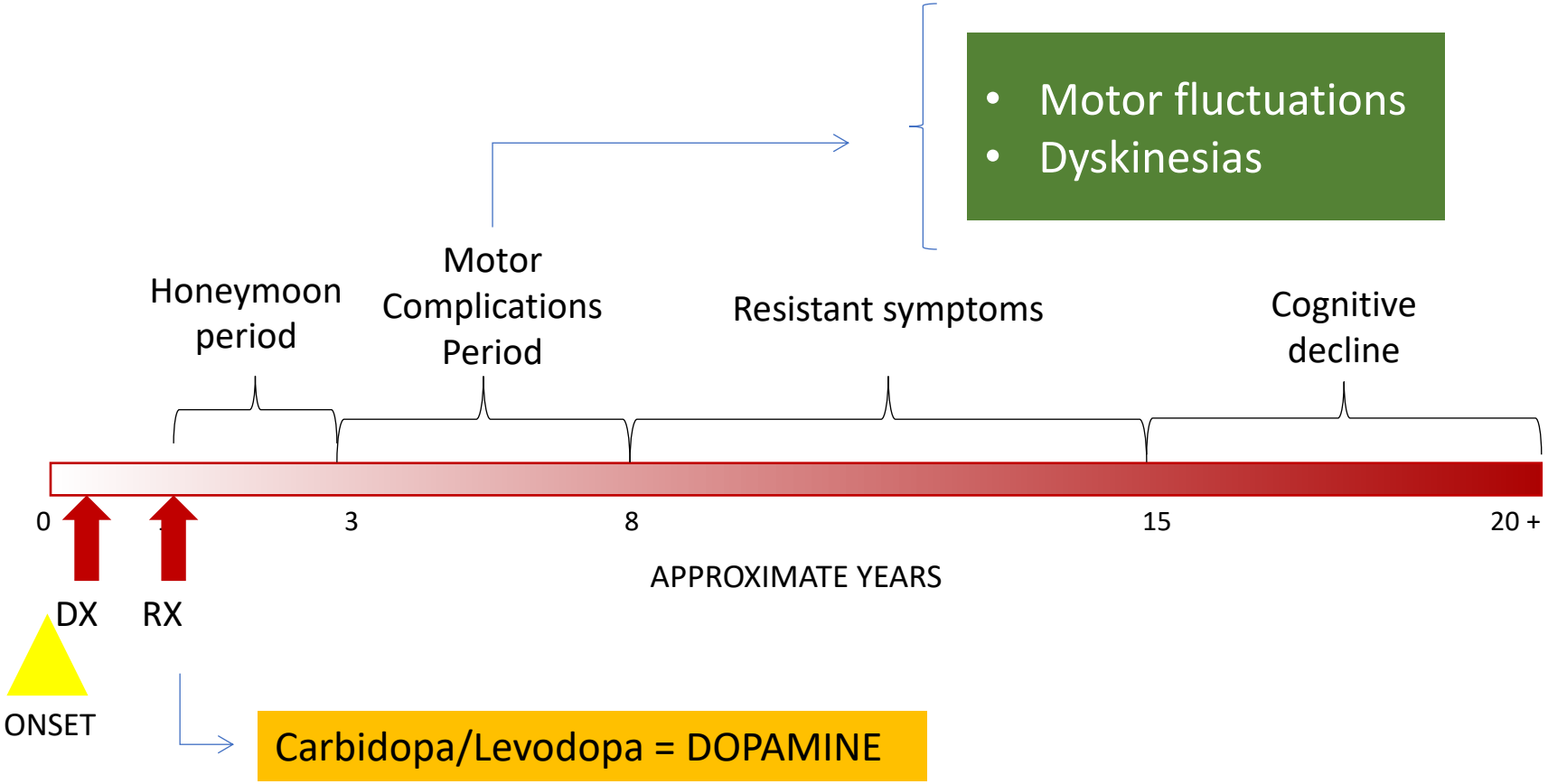
General approach to treat motor symptoms in PD

Figure 5. Proposed General Approach to Treating Motor Symptoms in Parkinson Disease

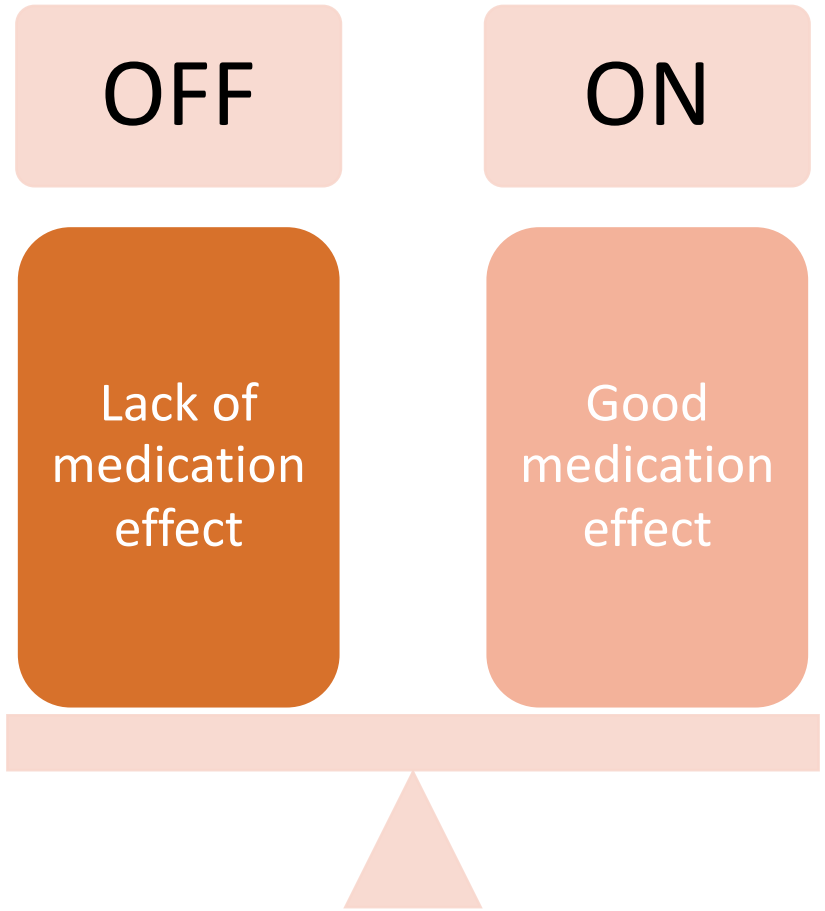


Armstrong M, Okun M. JAMA February 11, 2020. Volume 323, Number 6

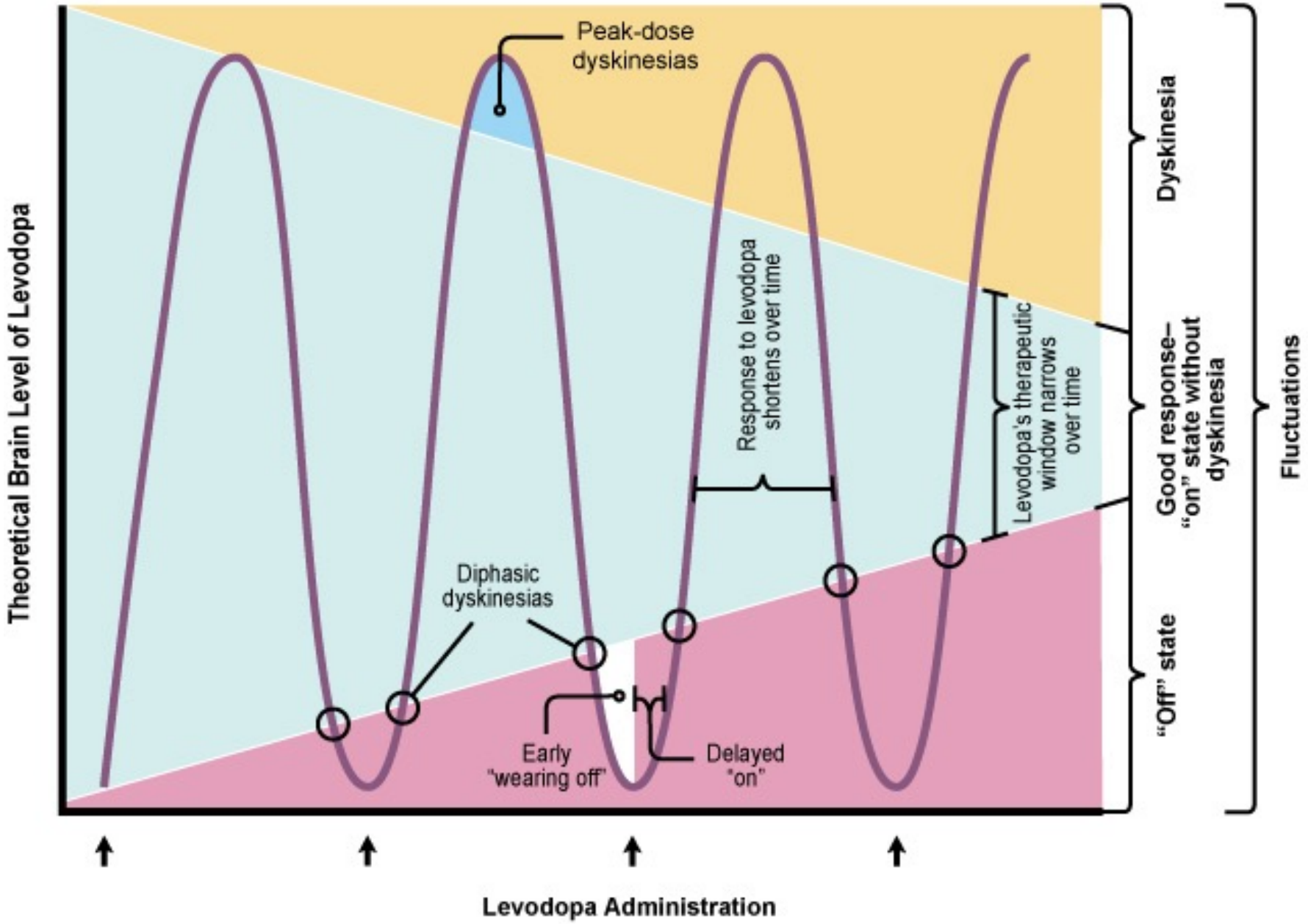
Progression of PD – despite best medical therapy



Features of motor fluctuations and dyskinesias



The therapeutic window of levodopa shortens over time



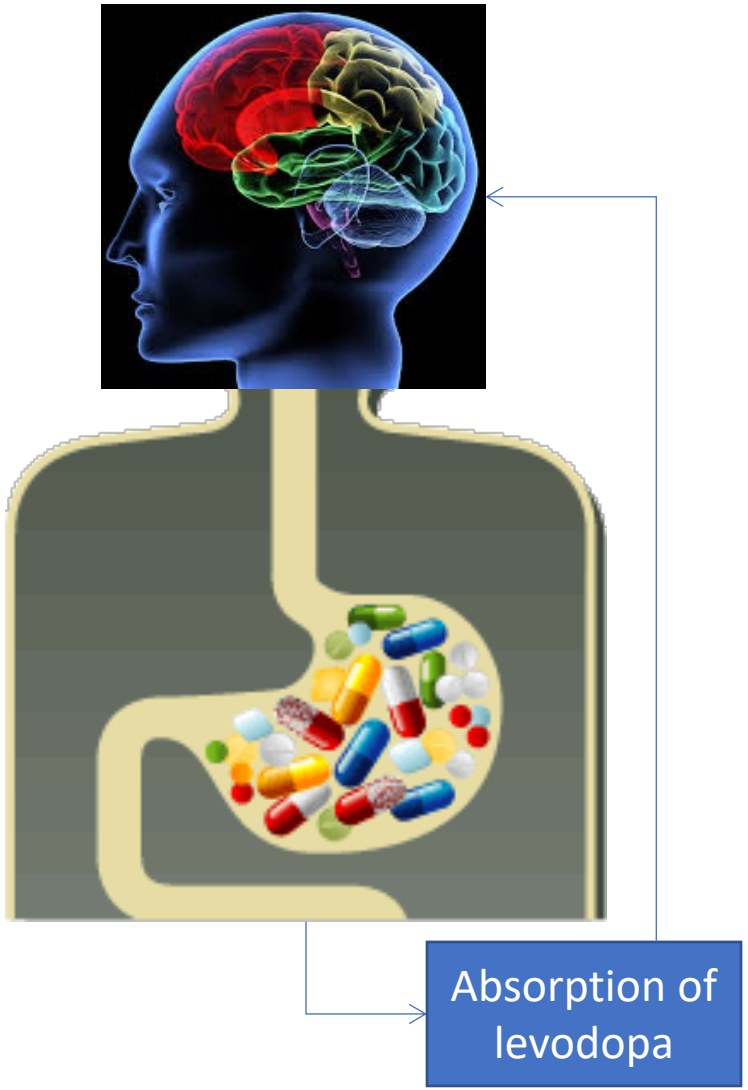
Delayed gastric emptying and high protein meals impair levodopa absorption and makes its action unpredictable

What slows gastric emptying?

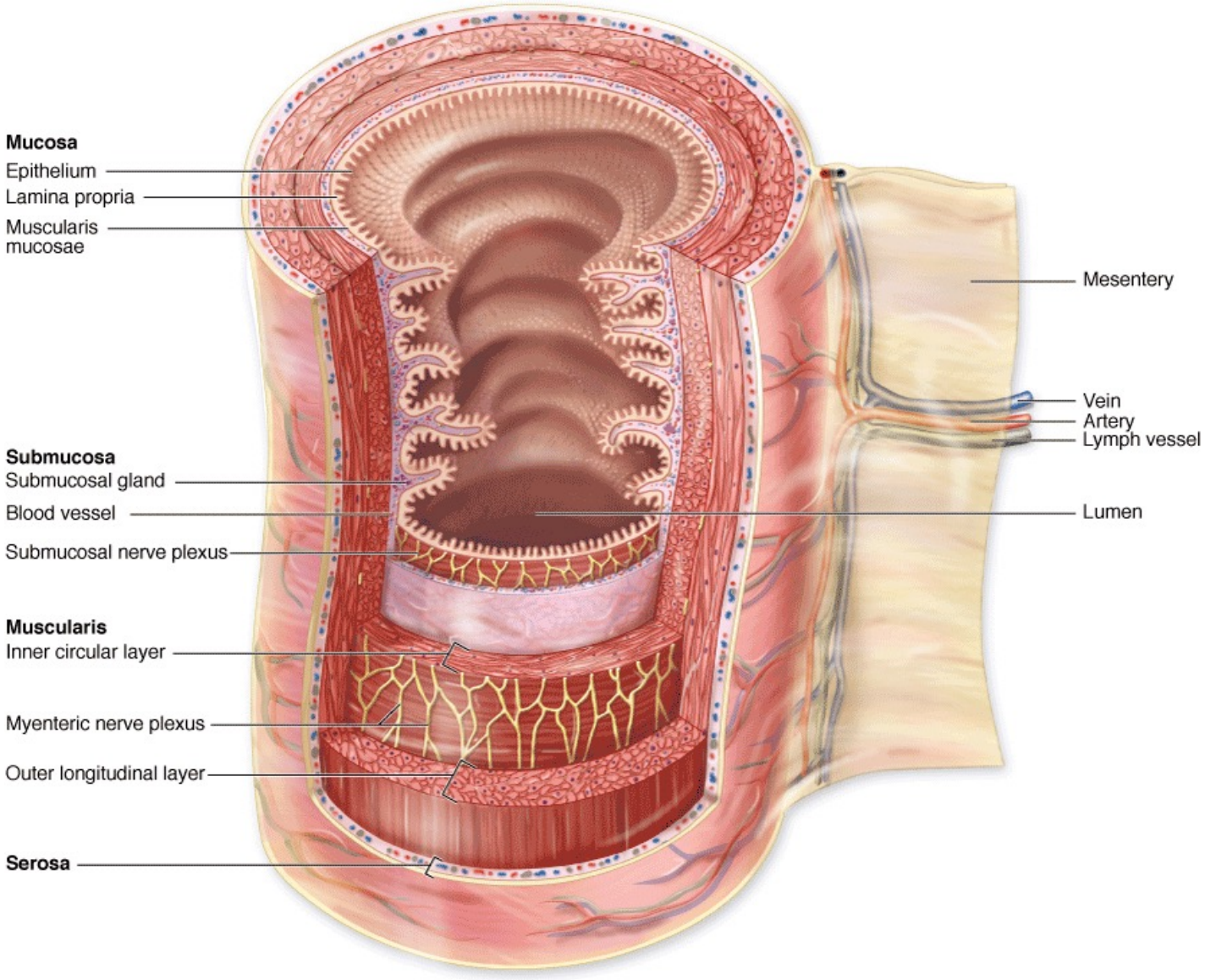
1. Damage of gastric/intestinal nerves
2. Levodopa itself
3. Dopamine agonists/anticholinergics
4. Fatty meals
5. High acidity of the stomach

What interferes with levodopa absorption once it passed to the intestine?

High protein meals



The Gastrointestinal Plexus (The Enteric Nervous System)



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

Alpha Synuclein in the Enteric Nervous System

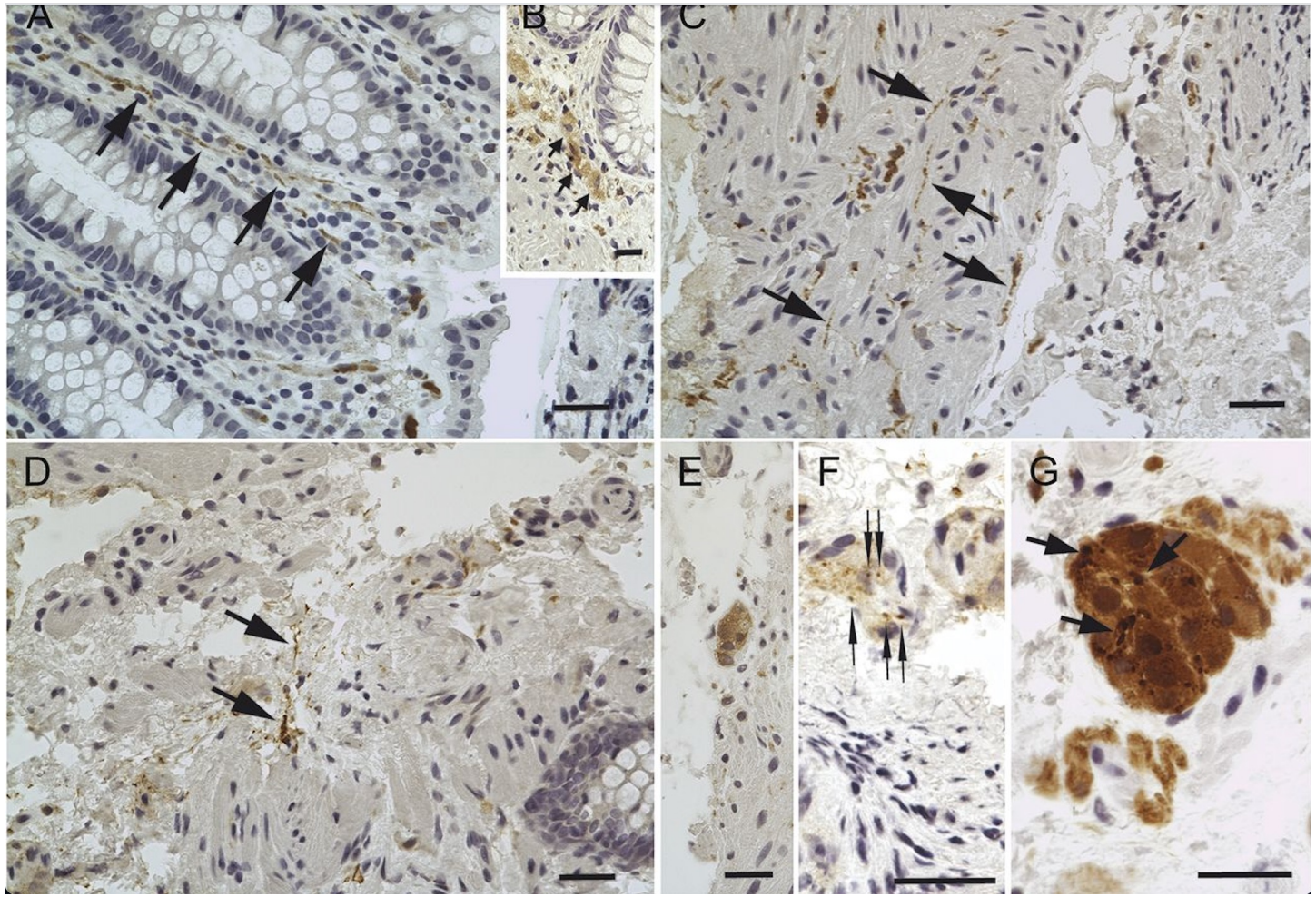


Figure 1 Patterns of 15G7 α-synuclein immunostaining in colonic biopsiesTotal α-synuclein expression in colonic biopsies detected with the 15G7 antibody. (A) α-Synuclein-positive nerve fibers (arrows) were identified in lamina propria of the mucosa. (B) α-Synuclein expression was detected with the 15G7 antibody in mucosal macrophages (arrows) in the lamina propria at the border to muscularis mucosae. (C) Immunopositive nerve fibers (arrows) were also commonly seen in muscularis mucosae. (D) α-Synuclein-positive nerve fibers (arrows) were detected in the submucosa of colonic biopsies. Submucosal ganglionic nerve cells showed variable pattern of α-synuclein immunostaining in the cytoplasm: (E) diffuse; (F) distinct punctate (arrows); or (G) coarse aggregate-like (arrows). Scale bars, 20 µm.

Sprenger F et al. Neurology 2015;85 (20)

Delay in gastric emptying

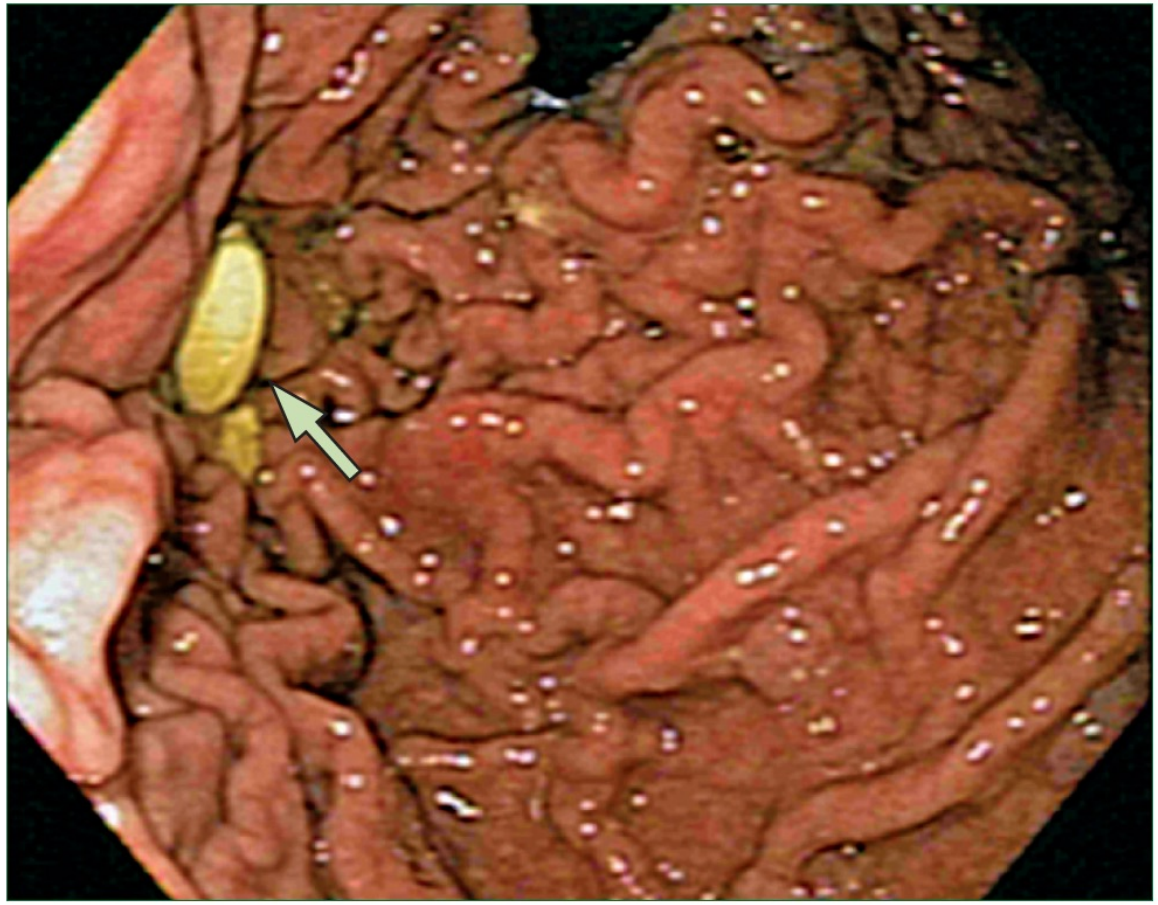


***Figure 2*: Delay in gastric emptying**
Photograph taken during gastroscopy. Arrow points to a carbidopa tablet remaining intact in a patient's stomach about 1·5 h after intake.

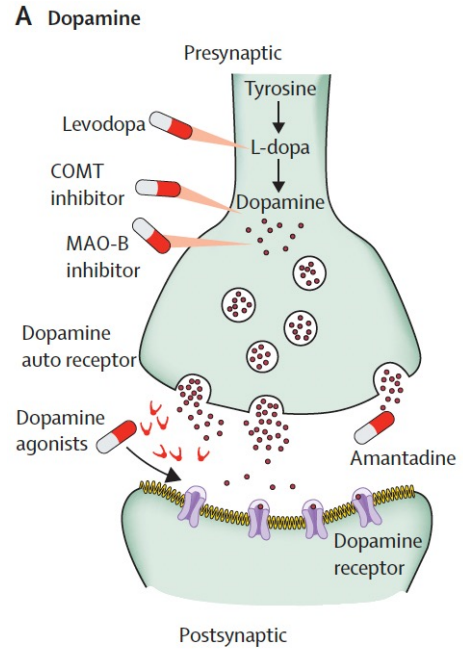
Fasano A et al. Lancet Neurol 2015;14:625-39

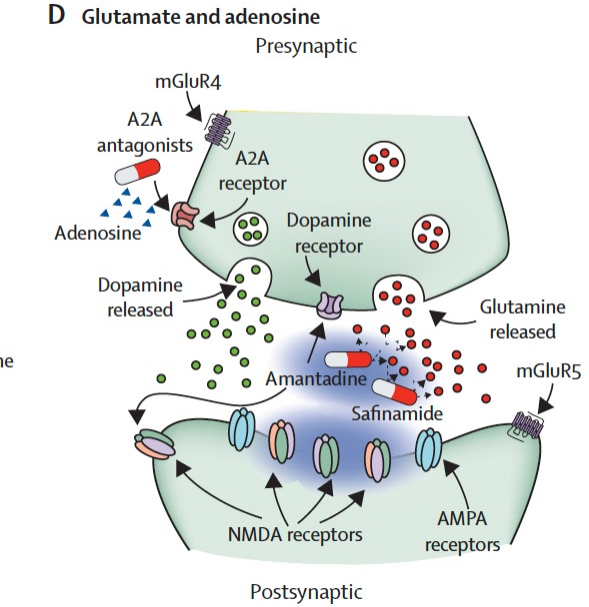
Treatment of predictable wearing off fluctuations: Loss of effect duration

- **More frequent CD/LD**

- **Medications that extend the duration of CD/LD**
  - Dopamine agonists (Ropinirole, Pramipexole, Rotigotine patch)
  - COMT inhibitors (entacapone, tolcapone, opicapone)
  - MAOB inhibitors (selegiline, rasagiline, safinamide)
  - A2A Receptors antagonists– Istradefylline (Nourianz)

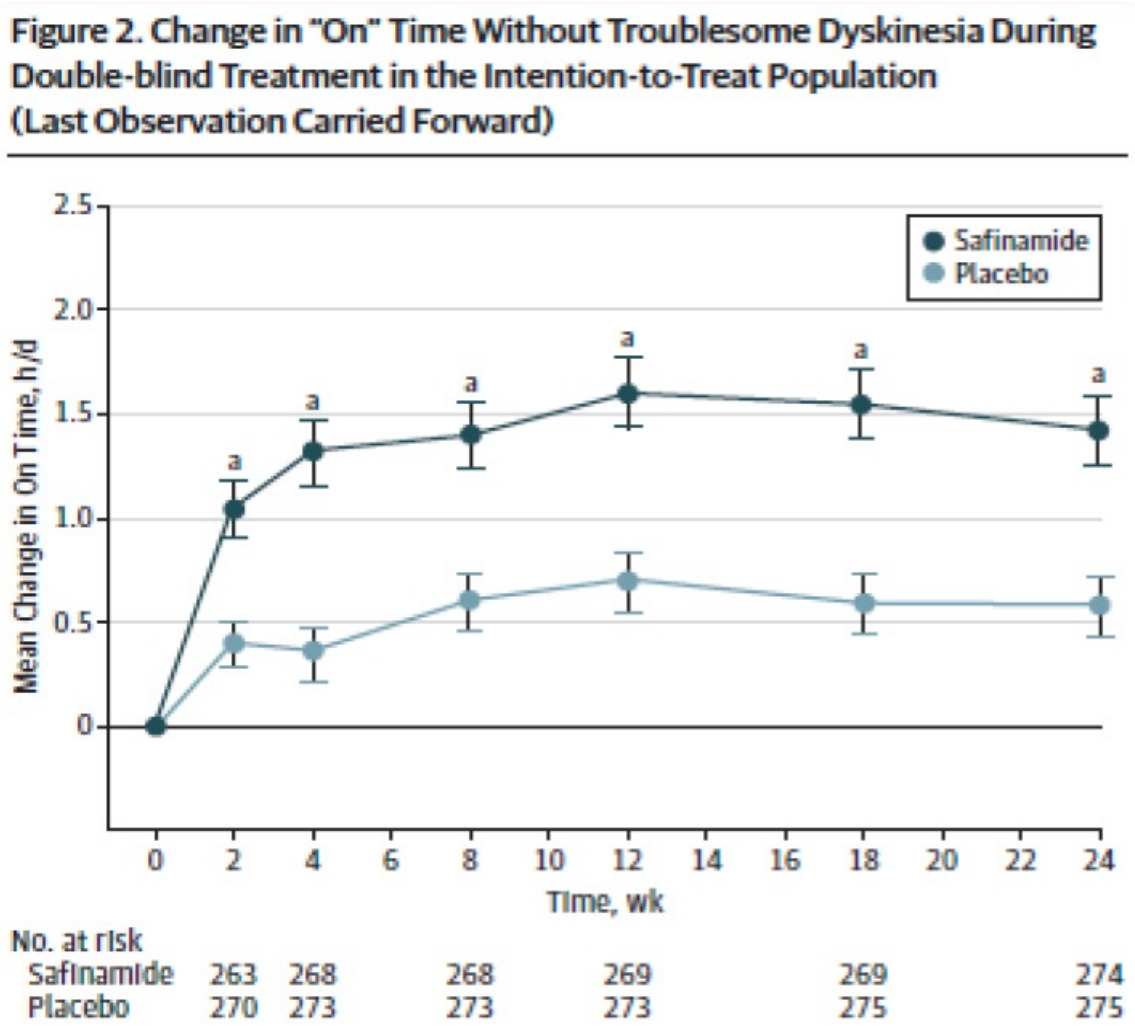
- **Extended-release Carbidopa/levodopa**
  - Rytary
  - IPX203 (not FDA approved yet)





Bloem B, Okun M, Klein C. The Lancet Neurology 2021

Safinamide (Xadago)



Manufacter: Newron Pharmaceuticals, Zambon, USWorldMeds

Mechanism of action
-Enhancement of dopaminergic function (MAO-B inhibitor)
-Inhibition of glutamate release
-Blocking sodium and potassium channels

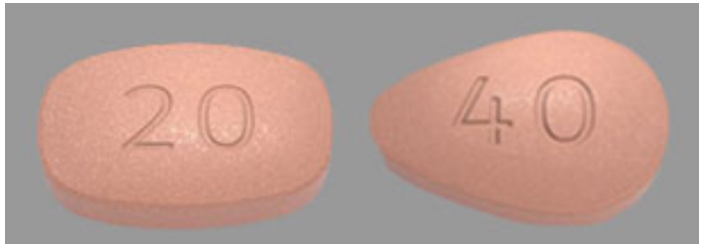
Dose: 50-100 mg per day

Pivot study
549 patients
Safinamide vs placebo x 24 weeks
Mean daily change in daily ON time without troublesome dyskinesia was +1.42 hrs for safimamide and +0.57 hrs for placebo

FDA approved in 3/21/17 as adjunctive treatment for patients with Parkinson's disease who experience OFF episodes while taking levodopa.

JAMA Neurol 2017;74(2):216-124

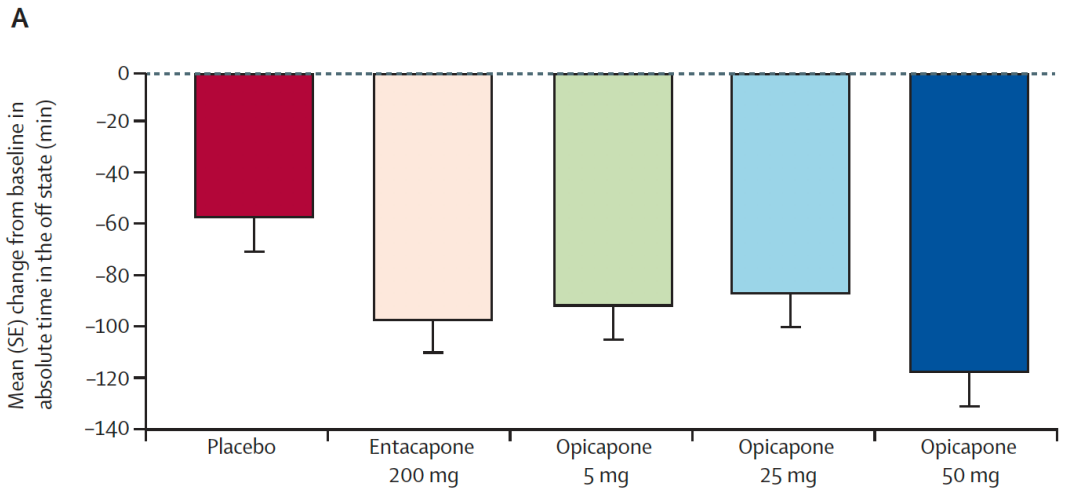
Istradefylline (Nourianz)



- Manufacturer: Kyowa Kirin, Inc
- Powerful and selective A2A receptor antagonist
- Without increasing dopamine levels, release the natural movement therefore increasing mobility.
- Taken once a day: starting dose is 20 mg, can be increased to 40 mg
- Considered as adjunct for patients with OFF time and dyskinesia (in some studies, it reduced off time without increasing dyskinesias).
- Tested in > 700 patients across multiple studies
- Reduces OFF time by an average of 1-1.5 hr per day
- FDA approved in August 2019

Hauser et al, Neurology. 2003 Aug 12;61(3):297-303; Mizuno et al. Mov Disord. 2010;25(10):1437-1443; Pourcher et al. Parkinsonism Relat Disord. 2012;18:178-184; Torti et al, Expert Opin Pharmacother. 2018 Nov;19(16):1821-1828; Stacy et al, Neurology. 2008 3;70(23):2233-2240

Opicapone (Ongentys)

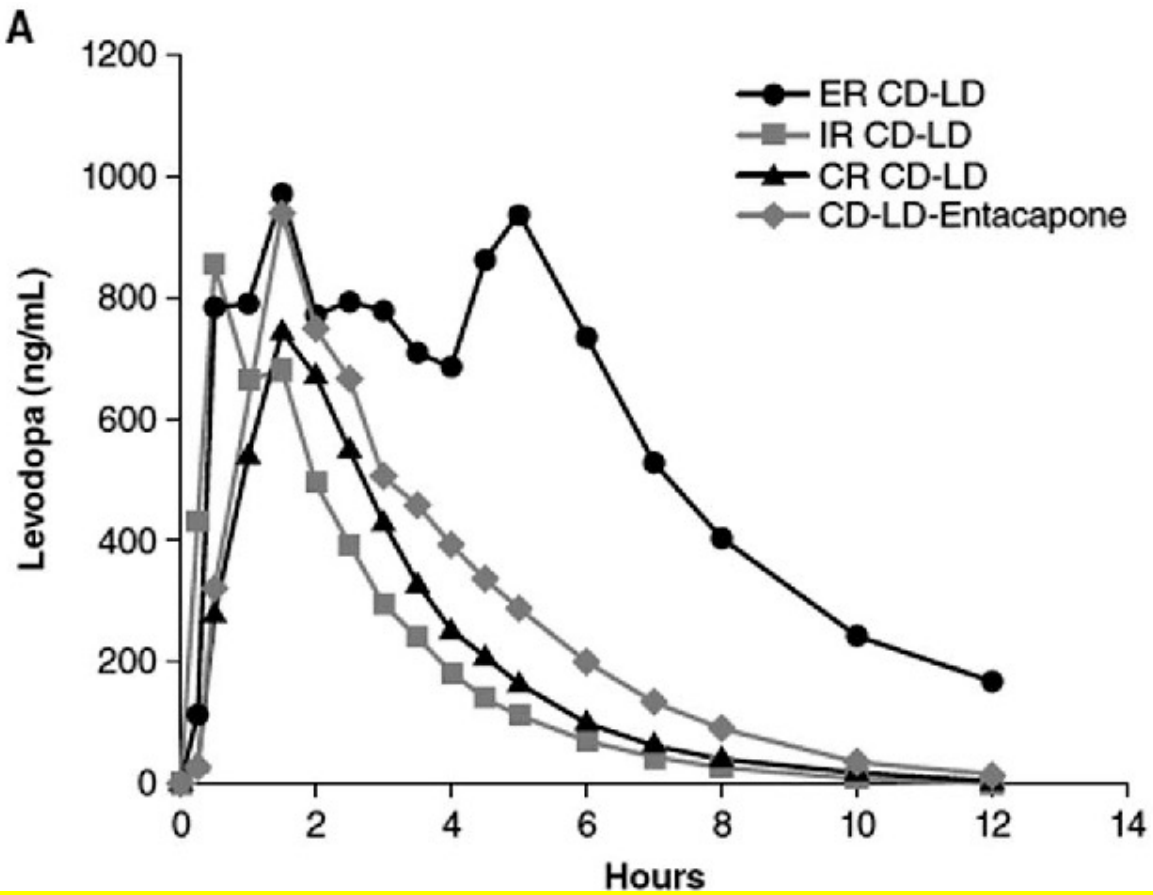


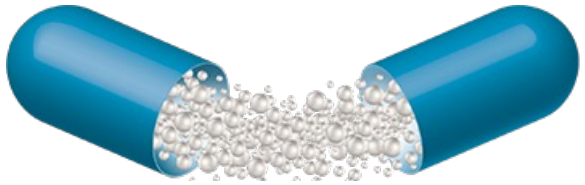
Bi-Park I Trial: Reduction in daily OFF time among treatment groups

- Manufacturer: Neurocrine Biosciences, Inc
- Action: Blocks COMT enzyme and extends levodopa effect.
- Taken as a once-daily pill (50mg) at bedtime, after the last dose of carbidopa/levodopa
- Consider as an add-on option to carbidopa/levodopa for patients experiencing end-of-dose OFF episodes
- In the largest trial to date, opicapone reduced OFF time by an average of almost 2 hours per day (compared to 1 hour in placebo group)
- FDA approved April 24, 2020

Ferreira et al, Lancet Neurol. 2016;15:154-165; Salamon et al, Expert Rev Neurother, 2019 Dec ;20(18):2201-2207

Carbidopa/levodopa extended release (Rytary)





IR beads:ER beads = 2:1

OFF time
Rytary: -2.2 hrs
CD/LD: - 1.0 hrs

ON time w/o or with non-troublesome dyskinesias
Rytary: + 1.8hrs
CD/LD: + 0.8 hrs

Improved ON time without troublesome dyskinesias and reduced OFF time.

Reduction in dosing from 5 to 3.6 doses per day

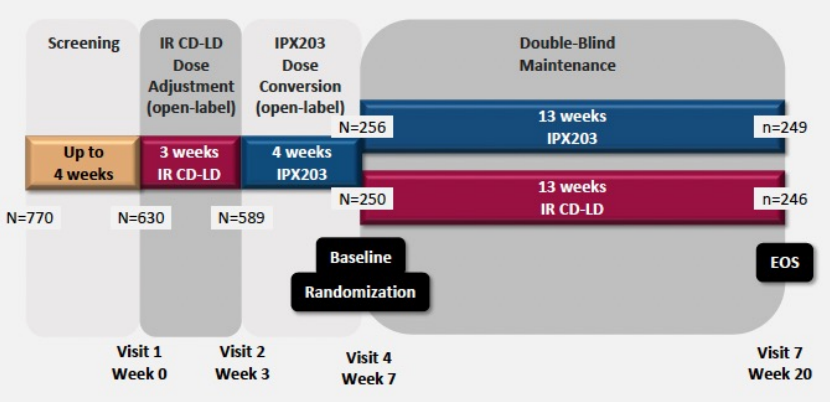
FDA approval: January 7, 2015

IMPAX / Amneal Pharmaceuticals LLC

Hauser et al. Lancet Neurol 2013;12:346-356

Motor fluctuations: IPX203 (RISE PD Trial)

Ph3, RCT, DB
IPX203: ER + IR CD/LD
Advanced PD >2.5hr OFF/day
1ry endpoint: Improvement in GOOD On time



RESULTS

IPX203: 0.53 hr more GOOD ON time, -0.48hr less OFF time, better PGIC (29.7 vs 18.8 very much or much improved. No changes in UPDRS 3 scores. (p=0.0194)
Dosing: 3/day vs 5/day

POST-HOC

IPX203 increased good ON time by 1.55 hr per dose (3.76hr vs 2.21) c/w IR CD/LD. (p<0.0001)

Table 1. RISE-PD efficacy results: Primary and key secondary endpoints

	Week 0 Enrollment	Week 7 Baseline (Randomization)	Week 20 End of Study (or Early Termination)	p-value
Mean "Good On" time (h)				
IPX-203	9.46	11.67	11.35	
immediate-release CD/LD	9.61	11.72	10.77	0.0194Δ
Mean "Off" time (h)				
IPX-203	6.15	3.95	4.18	
immediate-release CD/LD	6.05	4.02	4.75	0.0252Δ
Percentage of patients who reported "much improved" or "very much improved" scores on the PGI-C scale				
IPX-203	N/A	N/A	29.7%	
immediate-release CD/LD	N/A	N/A	18.8%	0.0015□
Mean MDS-UPDRS part III score				
IPX-203	29.6	26.9	27.8	
immediate-release CD/LD	29.7	27.0	28.0	0.9587Δ
Mean MDS-UPDRS Sum of part II + III score				
IPX-203	42.9	38.9	40.6	
immediate-release CD/LD	42.9	39.3	41.1	0.9668Δ

Δ = p-value based on change from Week 7 (Baseline) to Week 20 (End of Study or Early Termination [EOS/ET])
□ = p-value based on comparison of treatments at Week 20 (EOS/ET)

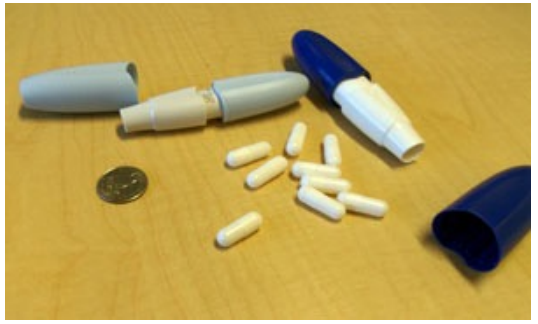
1. Hauser RA, Espay AJ, LeWitt P, et al. A Phase 3 Trial of IPX203 vs CD-LD IR in Parkinson's Disease Patients with Motor Fluctuations (RISE-PD). Presented at: AAN Annual Meeting; April 2-7, 2022; Seattle, WA, and virtual. Abstract 001225.
2. Hauser RA, Fernandez HH, Klos K, et al. Duration of Benefit Per Dose: Post Hoc Analysis of "Good On" Time Per Dose for IPX203 vs CD-LD IR in the RISE-PD Phase 3 Trial. Presented at: AAN Annual Meeting; April 2-7, 2022; Seattle, WA, and virtual. Abstract 001231.

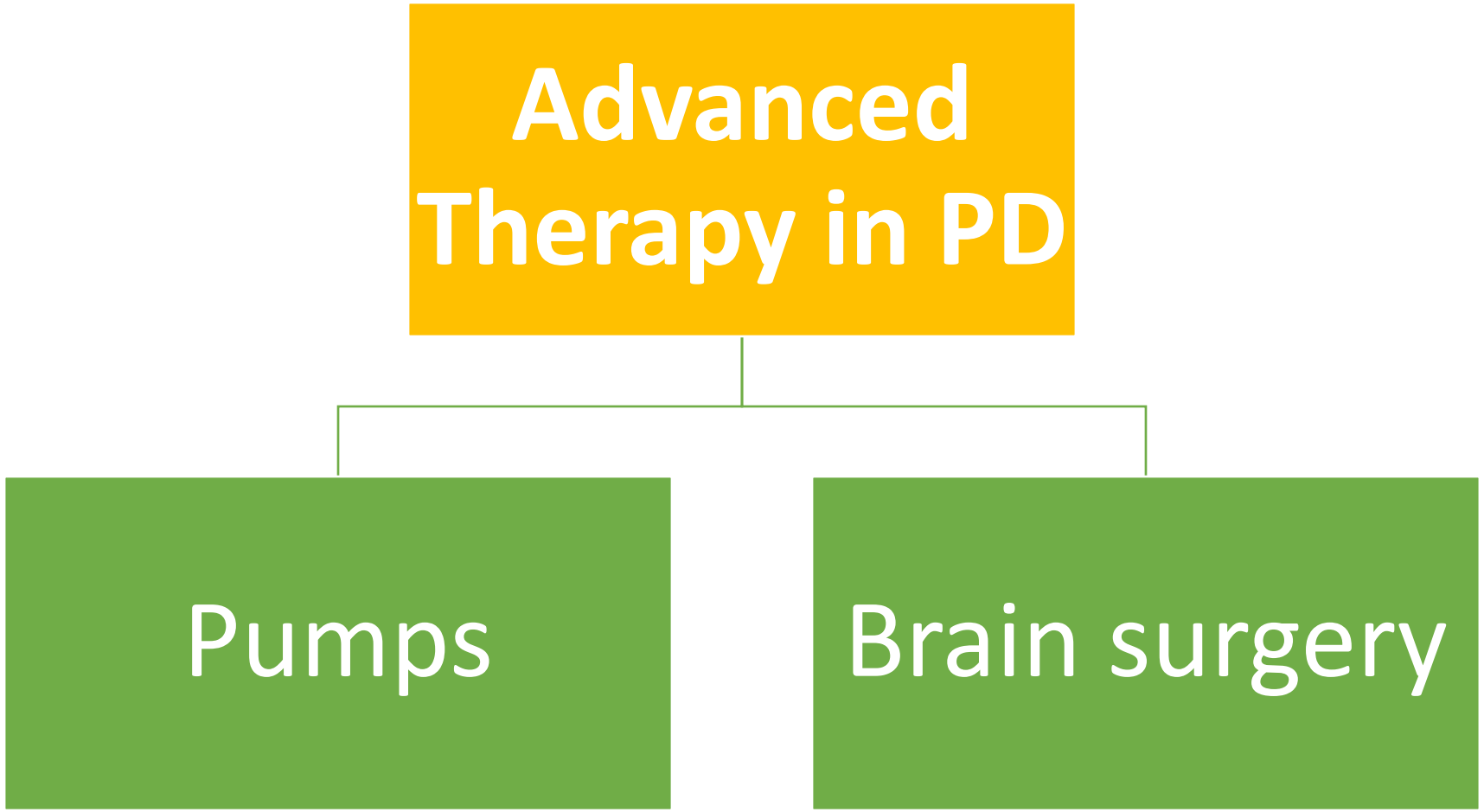
Rescue Therapy

- Apomorphine hydrochloride injection (Apokyn)

- Apomorphine sublingual film (Kynmobi)

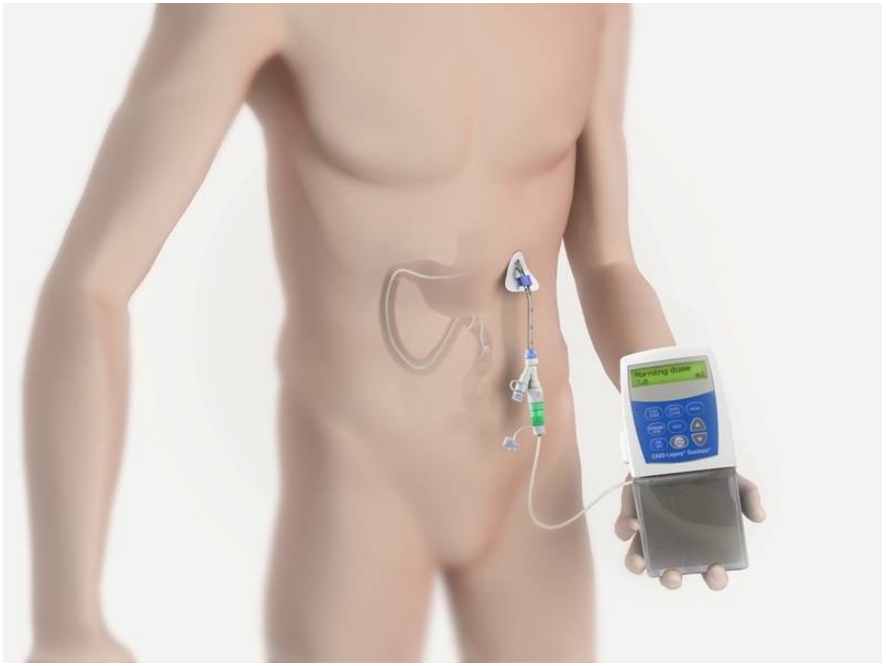
- Levodopa inhalation powder (Inbrija)




Advanced Therapy in PD
Pumps
Brain surgery

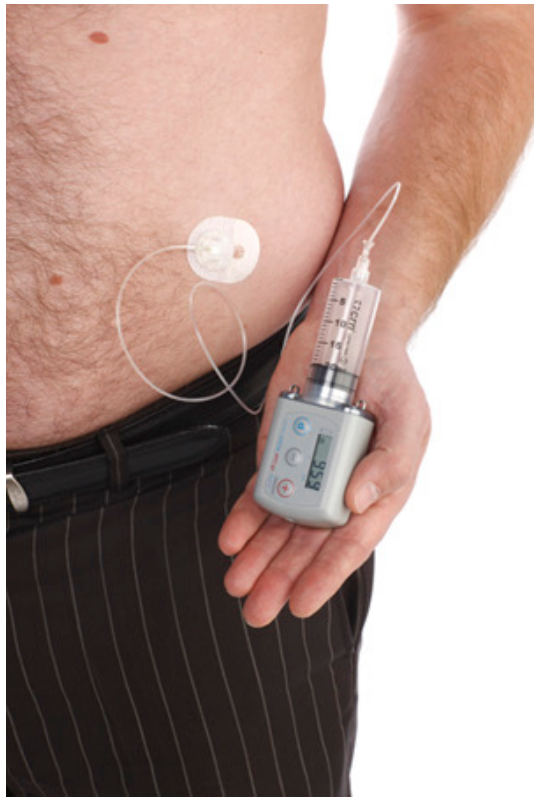
Pump treatment for Parkinson's Disease

Intestinal versus subcutaneous pumps



Duopa pump
Carbidopa/Levodopa enteral suspension enteral
4.463 mg/2020 mg per ml
Abbvie

VS

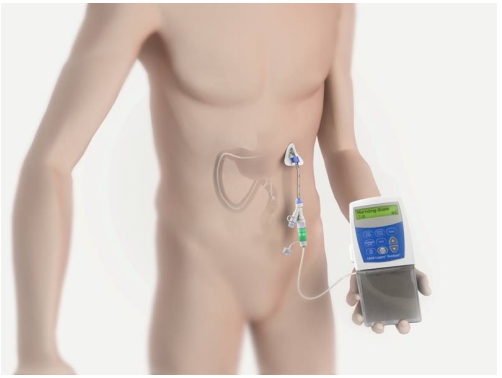


Apo-go pump
Apomorphine hydrochloride
Britannia Pharmaceuticals LTD

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced PD: a randomized, controlled, double-blind, double-dummy study

12 week, randomized, DB, double-dummy, double titration trial
Advanced PD + motor complications
26 centers in Germany, New Zeland and USA.
1:1 IR-CD/LD + placebo intestinal gel VS CD/LD intestinal gel + oral placebo
Primary end-point: Change from baseline to final visit in motor OFF time.

Results:
Reduction in OFF time: – 1.91 hr
Mean ON time: + 1.86 hr
Safety: 95% (35/37) CDIG vs 100% (34/34) IR CD/LD, mainly related to PGJ tube.



-PEG-J tube

-Cassette of Duopa:
2000mg LD/463 mg CD

-Pump
16hr infusion
Extra 20mg LD doses up to q2hr for rescue

-Abbvie pharmaceuticals

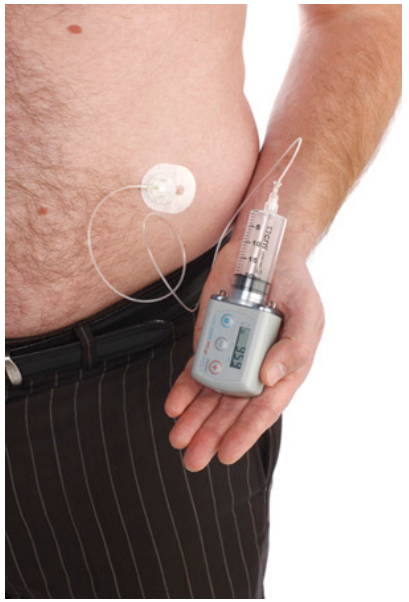
Olanow et al. Lancet Neurol 2014;13:141-49

Apomorphine subcutaneous infusion – TOLEDO trial

Placebo-controlled, double blind, multicenter trial (23 European hospitals)
PD >3 years with not adequately controlled motor fluctuations
1:1: 3-8 mg/hr apomorphine vs placebo infusion during walking hours (16 hr per day) for 12 weeks.
Primary end-point: Change in OFF time based on PD diaries

Results
128 patients screened, 107 randomized, 106 completed analysis (53 per group)
Reduction in OFF time was statistically significant: (p=0.0025)
- Apomorphine infusion (mean dose 4.68mg/hr): -2.47hr/day
- Placebo: 0.58 hr per day

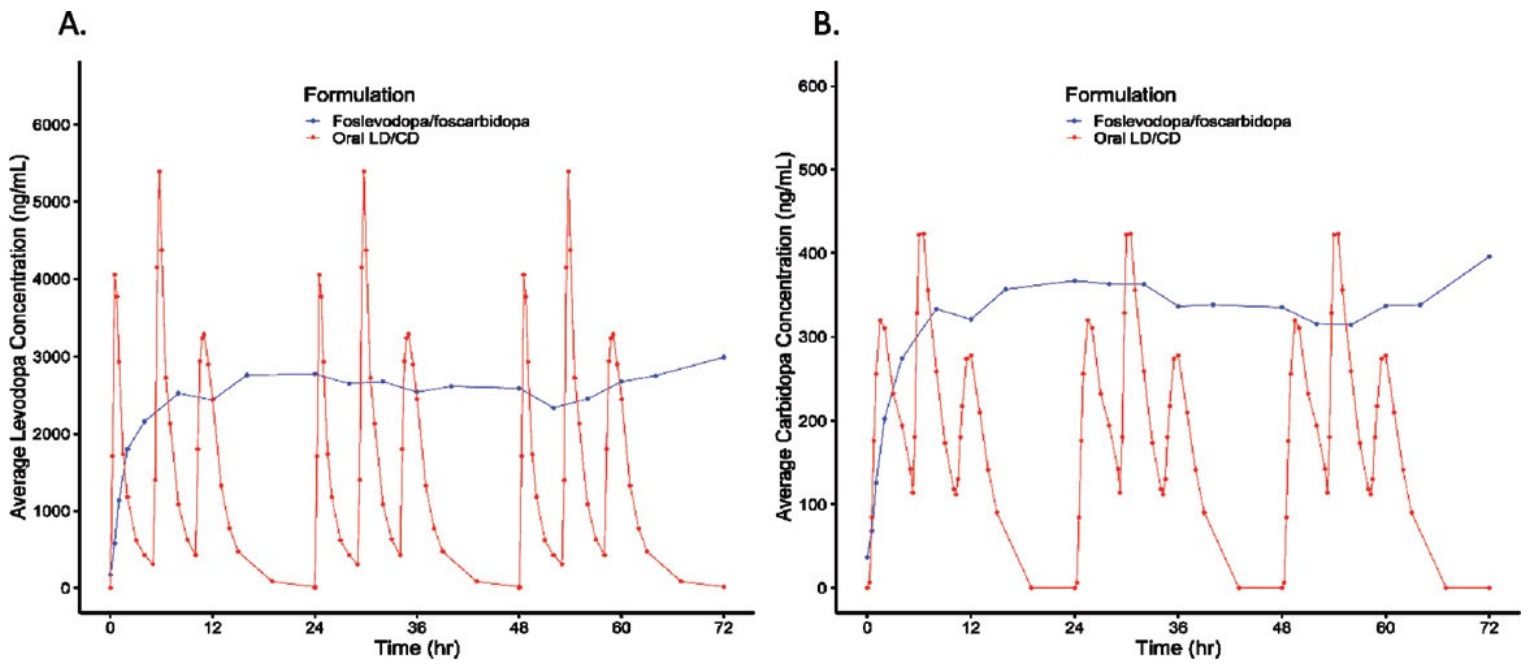
Apomorphine was well tolerated



Apo-go pump
Apomorphine hydrochloride
Britannia Pharmaceuticals LTD

Katzenschlager R, et al. Lancet Neurol 2018;17(9):749-759

ABBV-951 subcutaneous pump (Abbvie)



Foslevodopa/Foscarbidopa (ABBV-951 is a formulation of levodopa/carbidopa prodrugs with solubility that allows subcutaneous (SC) infusion.

Phase 1 study, single ascending dose, single-blind study.

28 male and female subjects

fLD/fCD was able to provide stable LD and CD exposures in PD patients over 72hrs via SC route of delivery with very low fluctuations in Ldopa.

Favorable safety profile.

Expected to be delivered continuously 24 hrs per day.

Rosebraugh M, Liu W, Neenan M, Facheris M. Journal of Parkinson Disease 11 (2021) 1695-1702

Motor fluctuations: Subcutaneous Foslevodopa/Foscarbidopa 24hr/d

Randomized, DB, double-dummy, active-controlled, Ph3 trial

Randomized 1:1 to fLD/fCD (prodrug) 24hr/day infusion (SQ pump) versus oral CD/LD over 12 weeks
74 patients fCD/fLD; 67 patients oral CD/LD

144 PD patients with 2.5 hr motor fluctuations
65 academic centers in USA and Australia

Primary outcome: ON time w/o troublesome dyskinesia

Results

Increment of good ON of 1.75 hr/day (2.72 vs 0.97, 95% CI 0.46 to 3.05; p=0.0083 vs CD/LD (and OFF time -1.79 hrs; 2.75 vs 0.96; (95% CI -3.03 to -0.54)

Adverse Events

85% fCD/fLD, 63% oral CD/LD (SAE: 8 vs 6%)
Infusion site AE: erythema 27%, pain 26%, cellulitis 19%, edema 12%).
Premature d/c study: 22% (fCD/fLD) vs 1% (oral CD/LD

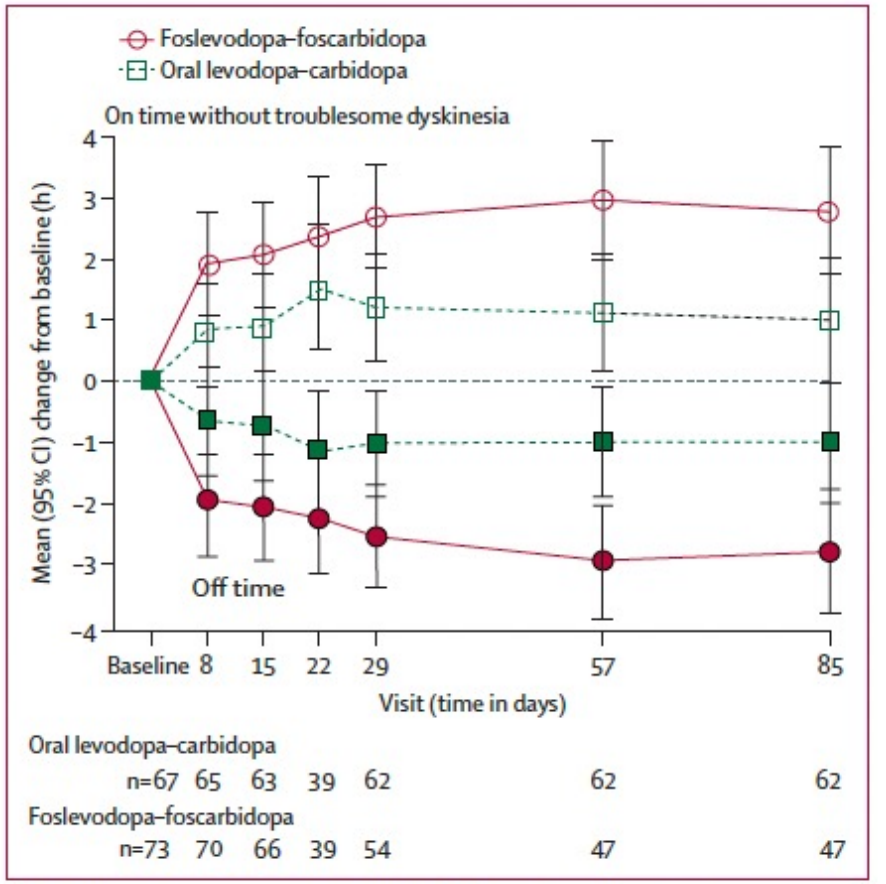


Figure 2: **Least squares mean (95% CI) of change from baseline in average daily on time without troublesome dyskinesia and off time (full analysis set)** Assessed using a 24-h Parkinson's disease diary and normalised to a 16-h waking day. On time without troublesome dyskinesia is the sum of on time without dyskinesia and on time with non-troublesome dyskinesia. Error bars represent the 95% CI of the least squares mean change from baseline. Day 22 was an optional visit at the investigator's discretion and based on the participant's Parkinson's disease symptoms.

M Soileau, et al. Lancet Neurol 2022;21:1099

Subcutaneous Levodopa: ND0612 (Neuroderm)

- Continuous subcutaneous infusion of levodopa using a pump
- 24hr infusion pump
- Poor levodopa solubility has precluded this approach
- ND0612 is an investigational drug-device combination that has been designed to continuously deliver liquid levodopa/carbidopa (60/7.5 mg/mL) by subcutaneous infusion.

- Two previous pharmacokinetic studies in PD patients with motor fluctuations have demonstrated that ND0612 maintains steady, therapeutic levodopa plasma concentrations [1,2]

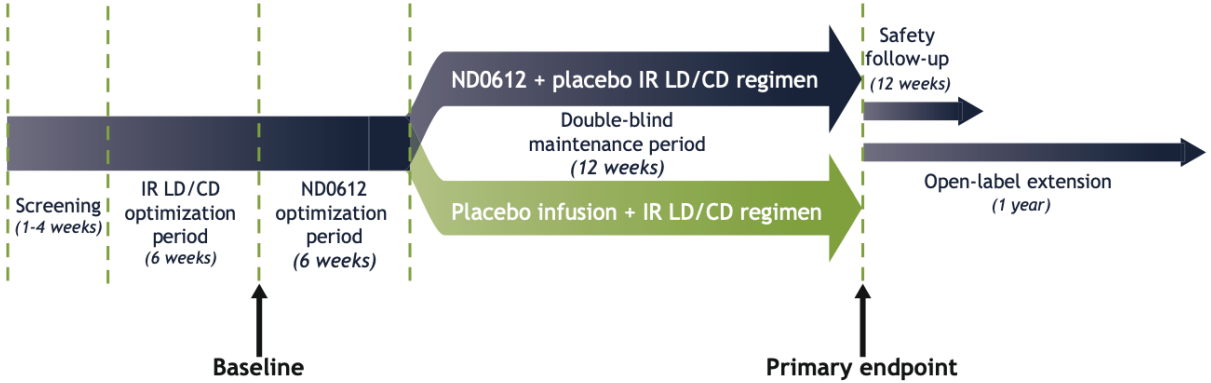
- A small Phase II 28-day open label efficacy study (n=38) showed that infusion of ND0612 significantly reduced daily OFF time by 2.8 hrs. and morning akinesia while increasing 'good ON' time by 3.7 hrs compared to baseline in the 24hr as opposed to 14hr infusion group.[3]

1.Giladi N,Caraco Y,Gurevich T, et al. Pharmacokinetic profile of ND0612(levodopa/carbidopa for subcutaneous infusion) in Parkinson's disease (PD) patients with motor fluctuations: results of a Phase IIa dose finding study (Abstract). Mov Disord 2015;30 (Suppl 1).
2. Giladi N, Caraco Y, Gurevich T, et al. ND0612 (levodopa/carbidopa for subcutaneous infusion) achieves stable levodopa plasma levels when administered in low and high doses in patients with PD [abstract]. Mov Disord. 2017; 32 (suppl 2).
3. Poewe W, Stocchi F,Simuni T, et al. A multicenter, parallel-group, rater-blinded, randomized clinical study investigating the efficacy, safety and tolerability of 2 dosing regimens of ND0612. (Abstract). Mov Disord 2018;33:S92-93.

ND0612 (Neuroderm) – Ph 3 - Boundless Trial

Phase 3 trial Boundless Trial

Study design: A multicenter, randomized, active-controlled, double-blind, double-dummy, parallel group clinical trial



Boundless trial: ND0612 is administered (2 infusion sites) over 24 hrs to a total LD/CD dose of 720/90 mg per day
-RCT – Double blind/double dummy – PC
-PD <=3, >=2.5 hr OFF/day
-1:1 ND0612 vs IR CD/LD x 12 weeks
-n= 259 (128 ND0612 vs 131 IR CD/LD)
-1ry endpoint: GOOD ON TIME
-94% completed study

Results: ND0612
Increased ON time: 1.72hr (-0.48 vs -2.20)
Reduced OFF time: -1.40 hr
Improved UPDRS 2
Improved PGIC: OR 5.31
Improved CGIC: OR 7.23

TEAEs
89% of 322 patients
103 (80%) ND0612 vs 131 (64%) IR CD/LD
-Infusion site rxn: 83% (open label dose optimization, 57% ND0612 vs 43% IR CD/LD) > most were mild.
-SAE: ND0612 (2 cellulitis, 1 abscess/ulcer, 1 tingling/sensory motor neuropathy). One death ND0612 > unrelated to study drug > fall and TBI).

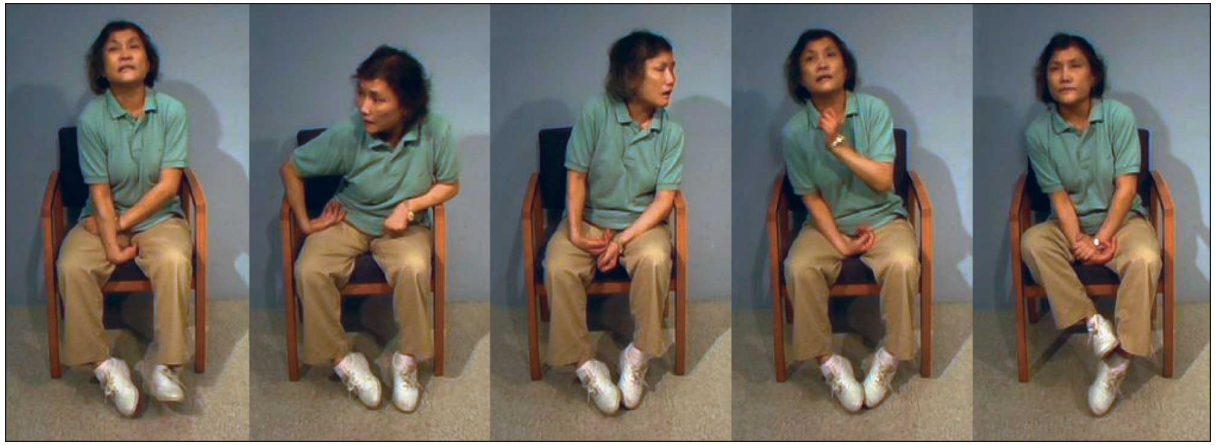
Ongoing OL extension trial

Unpublished - Espay A et al. The Lancet Neurology 3/15/24

Management of Dyskinesias

MILD AND NON-BOTHERSOME
No treatment

BOTHERSOME
Treatment advised:
- Reduction in dopaminergic medications
- Anti-dyskinesia medications
- Deep brain stimulation



The frequency of levodopa- and dyskinesia-induced motor complications increases with disease progression and is grossly estimated at 10% per year after initiation of levodopa therapy.

Based on several epidemiological studies, patients younger at the onset of the disease, with longer use of levodopa and with higher individual doses have an increased risk of developing motor complications.

Amantadine extended release (Gocovri)

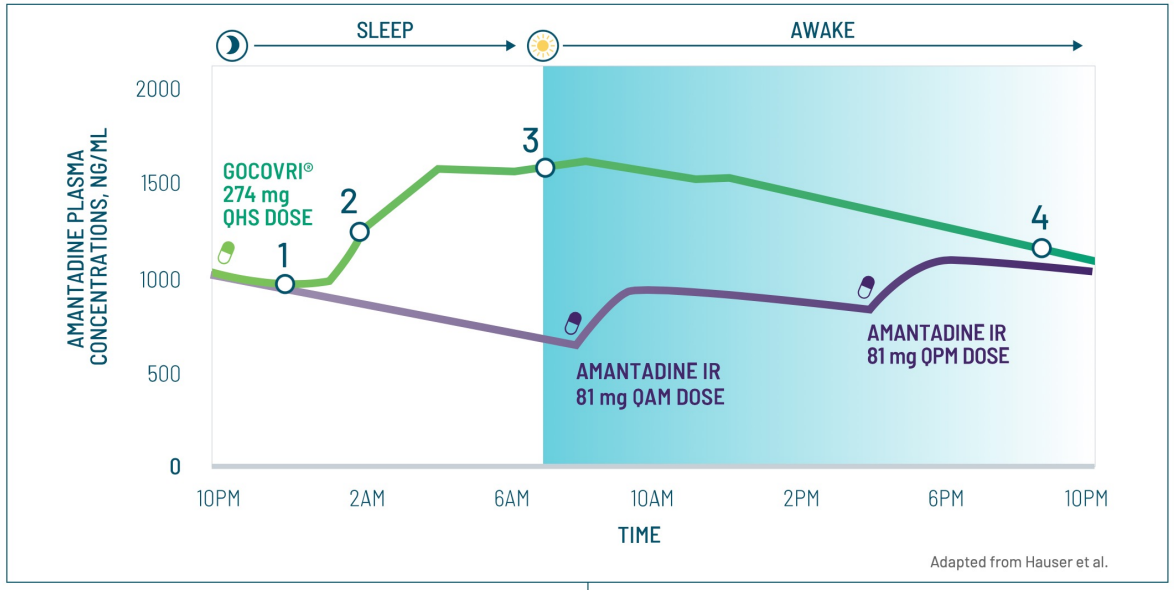
Manufacturing: ADAMAS Pharmaceuticals

Effect: Reduces dyskinesias by possibly blocking NMDA receptors in striatum

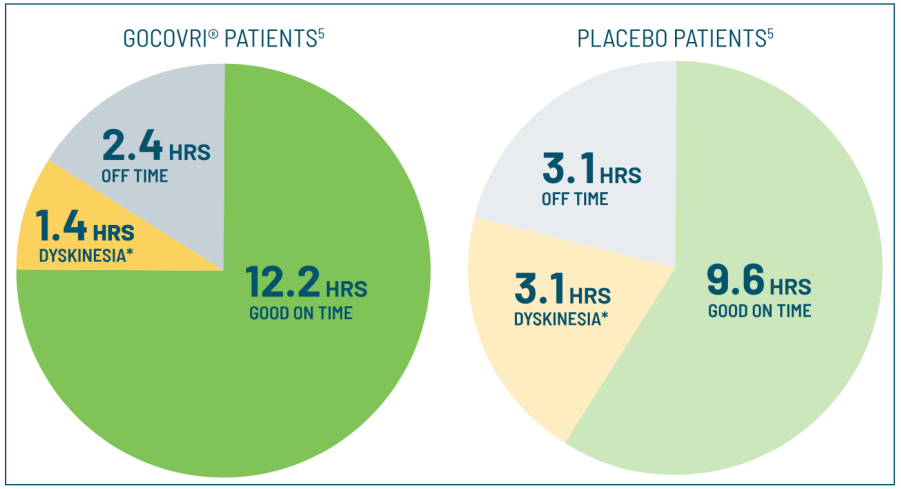
Studies
EASE LID 1: Ph 3, 24 weeks, n = 121
EASE LID 2: Ph3, 13 weeks,, n=75
Open label EASE LID 2: Sustained efficacy for at least 2 years
Gocovri 274 mg vs placebo
Primary endpoint: Change in UDysRS from baseline to week 12

Results at week 12
Reduced dyskinesias (UDysRS): -17.7 (Gocovri) vs -7.6 (placebo): 27 % improvement
Reduction in OFF time: + 0.4 hrs (placebo), - 0.6hrs (Gocovri): 36 % improvement
Increased good ON time: + 3.8 hrs (Gocovri) vs +1.4 hrs (placebo): 29% improvement

FDA approval
Aug 24, 2017: Anti-dyskinesia
Feb 2, 2021: Adjunctive treatment to CD/LD for PD related OFF



POOLED PATIENT DIARY RESULTS FROM STUDIES 1 AND 2 (AT 12 WEEKS)[5]



*Dyskinesia defined as ON time with troublesome dyskinesia.
GOOD ON time = ON time without troublesome dyskinesia.
Pooled baseline values (hours) for dyskinesia, OFF time, and GOOD ON time, respectively:
Placebo: 5.2, 2.6, and 8.1, GOCOVRI®: 4.7, 3.1, and 8.5[5]

EASE LID: Pahwa R et al. JAMA Neurol 2017 Aug 1;74(8):941-949
EASE LID 2: Hauser RA, et al. J Parkinsons Dis. 2017;7(3):511-522
EASE LID 2 – OL: Tanner CM, et al. J Parkinsons Dis 2020;10(2):543-558

Surgical treatment of PD

Irreversible:

Thalamotomy

Pallidotomy

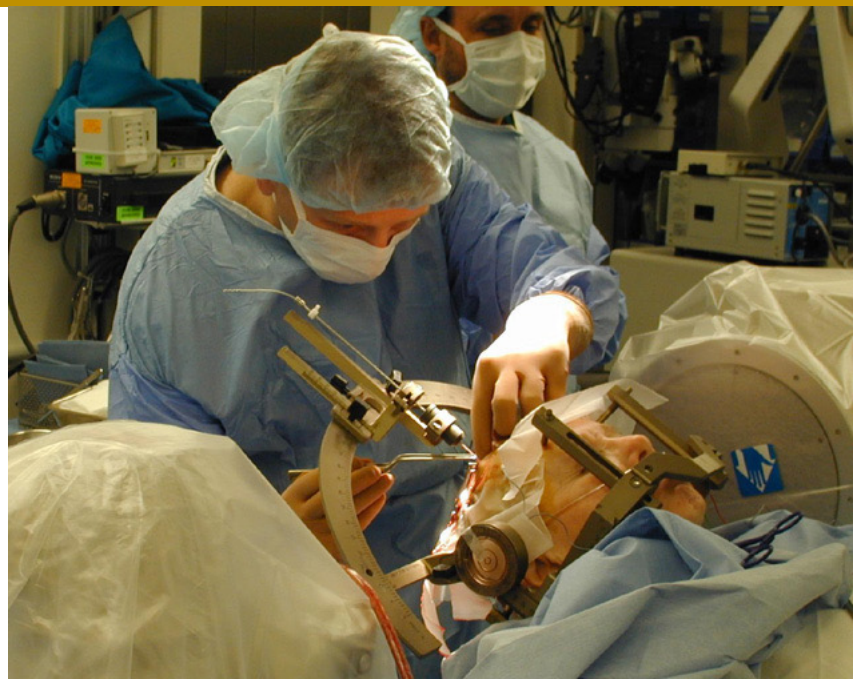
Subthalamotomy

MR guided US thalamotomy

MR guided US subthalamotomy

Reversible:

Deep brain stimulation (DBS)



Deep Brain Stimulation (DBS)

-Approved by the FDA for the treatment to PD since 2002.

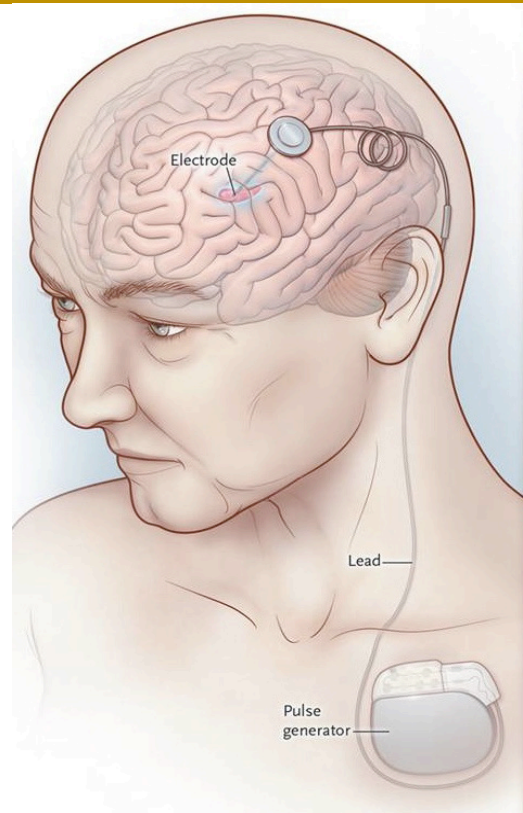
-A special wire, called lead is inserted into a specific area of the brain.

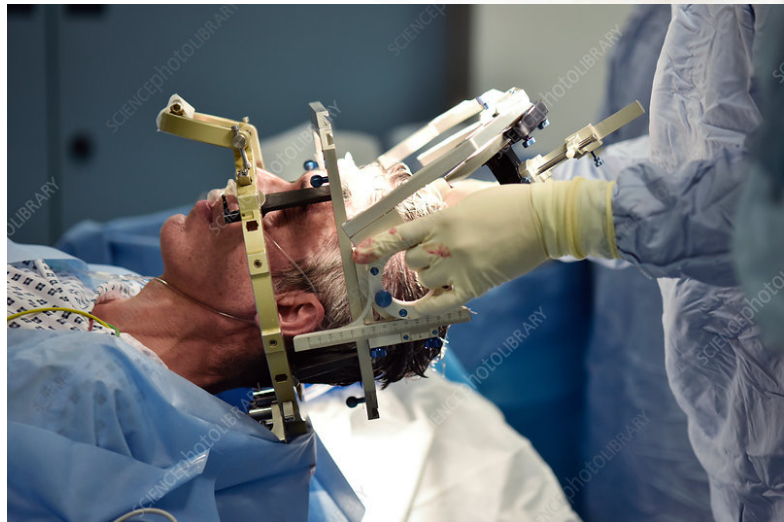
-The lead that has four electrodes delivers currents to precise brain locations responsible for movement, regulating the abnormal brain cell activity that causes the symptoms.

-It does not cure or slow down the progression of the disease.

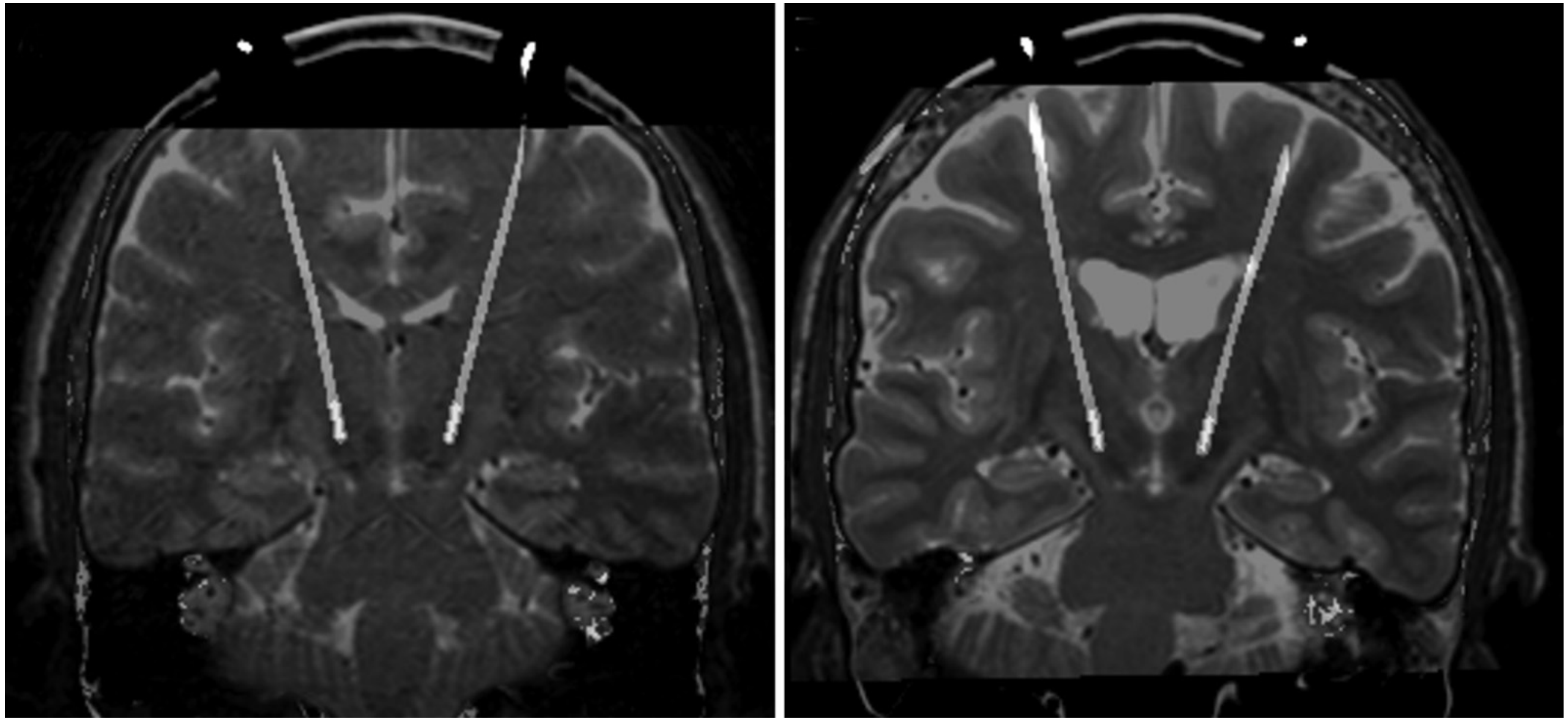
-DBS is better than the best medical therapy to treat the motor symptoms of PD.

- 4hr reduction in OFF time per day
- Reduction in the levodopa dose up to 50%





BIL STN lead implants



Coronal reconstruction from preoperative MRI with postoperative CT and identification of DBS leads

DBS for Parkinson's disease

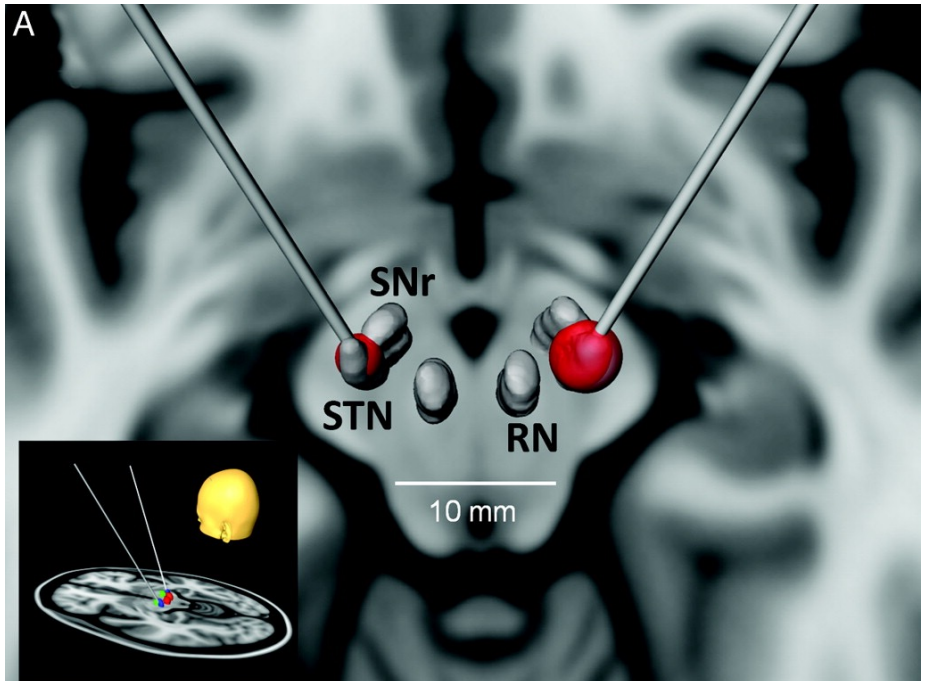
(Over 100,000 people implanted worldwide with DBS therapy)

Targets:

- STN (Subthalamic Nucleus)
- Gpi (Globus Pallidus Pars Interna)

When to introduce the Therapy?

- Levodopa induced dyskinesias
- Unexpected OFF periods – motor fluctuations (medication effect duration is not longer sustained)
- Tremor refractory to medications



When to introduce DBS Therapy in PD?

Window of opportunity

Oral therapies controlling symptoms

Oral therapies lose effectiveness

When symptoms no longer respond to oral therapies. The patient is not longer a DBS therapy candidate.

What Parkinson's disease symptoms respond?

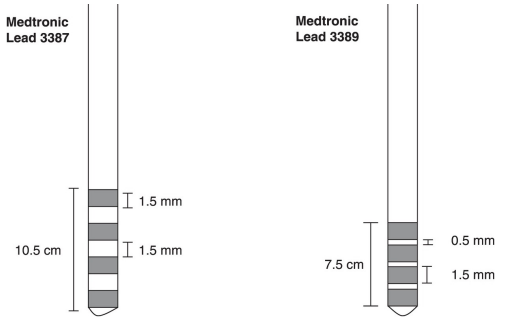
Good response to DBS
Bradykinesia/slowness
Tremor
Rigidity
Dyskinesias
Wearing off

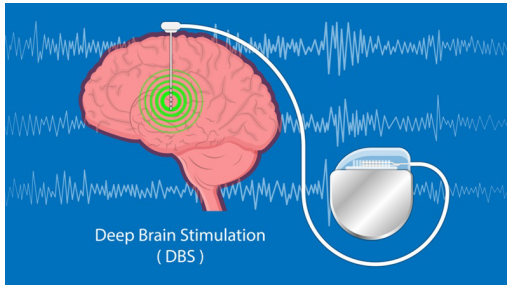
Resistant to DBS
Speech
Balance
Freezing of gait
Handwriting

Not improved by DBS
Dementia
Depression
Psychosis
Constipation
Urinary urgency
Sleep

DEEP BRAIN STIMULATION - PLATFORMS

Medtronic



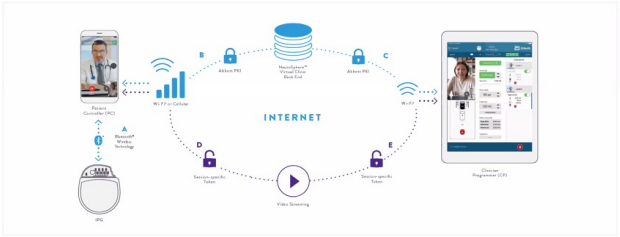


Abbott
A Promise for Life

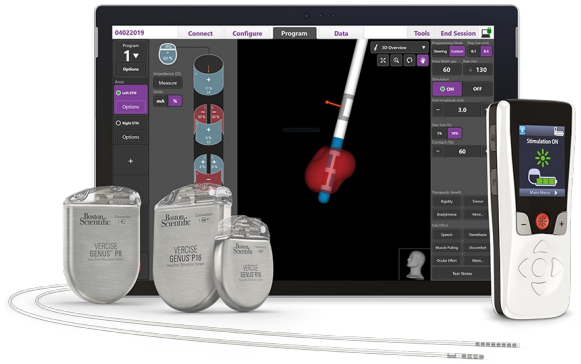
ST. JUDE MEDICAL

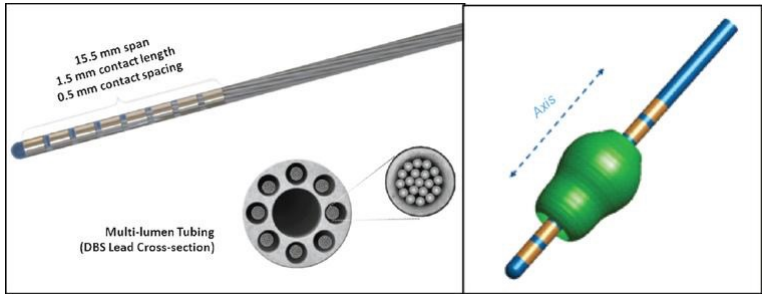
SECURE PLATFORM BACKEND

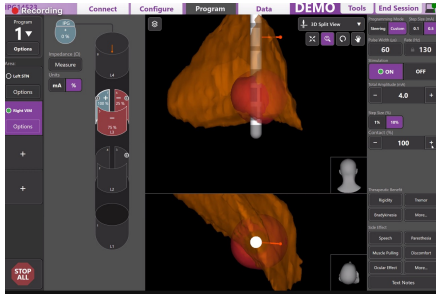
NEUROSPHERE™ VIRTUAL CLINIC
PLATFORM BACKEND TO SET UP A SECURE PROGRAMMING SESSION WITH INTEGRATED VIDEO



Boston Scientific
Advancing science for life™

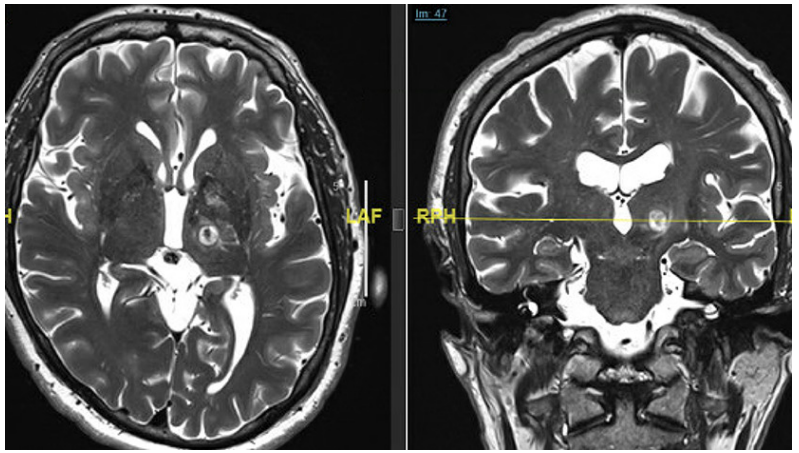






MR guided Focused Ultrasound

- Uses MR guidance for precision transcranial delivery of high intensity focused ultrasound energy to create a thermal tissue ablation.
- Tissue temperature and lesion size can be monitored in real time.
- Benefits and side effects can be monitored in real time.
- Unilateral MRgfUS of VIM-thalamus was FDA approved for medication refractory ET in 2016. Since 2023, 2nd side can be performed 9m later.



INDICATIONS

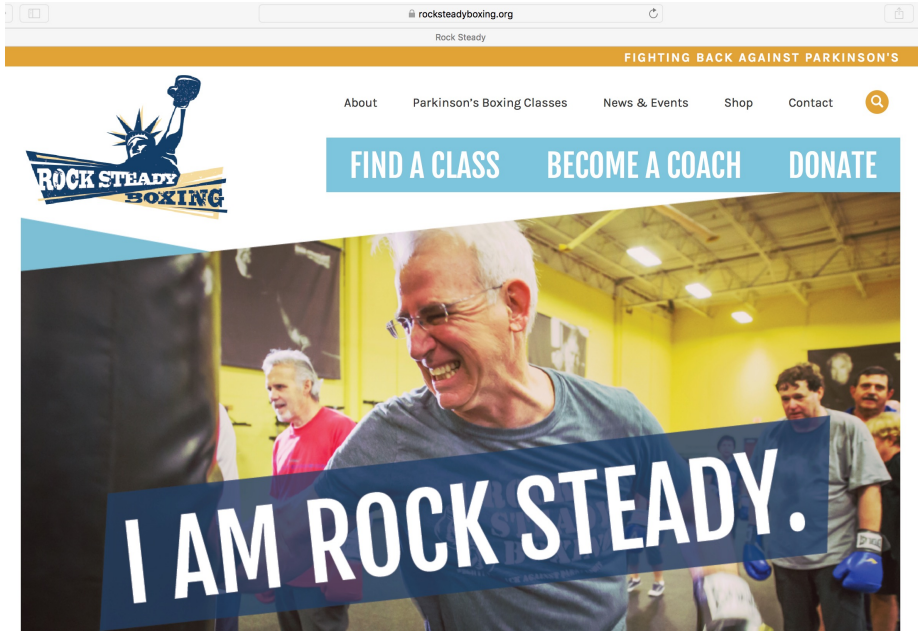
2018: PD tremor: 2018, thalamic VIM

2021: PD slowness, rigidity, dyskinesia, GPI

Other therapies in PD

Alternative Therapy
-Cannabis
-Yoga
-Glutathione
-Music
-Exercise
-Dance
-Boxing

Therapies
-Physical: LSVT – BIG, balance therapy
-Occupational: Improve activities of daily living, driving evaluation
-Speech and Swallowing: LSVT-LOUD, swallowing evaluation



Walking aids and wheelchairs
-Cane
-Walker
-Scooters
-Wheelchair (mechanical or electric)

What else is in the pipeline for PD motor symptoms?

TO SLOW DOWN PD

- Targeting α-Synuclein (inhibition of misfolding, aggregation, immunotherapy)
- Agonists of GLP-1 receptor (Exenatide, NLY01, liraglutide, lixisenatide, semaglutide)
- Antioxidants (Idebenone, gluthatione, N-acetylcysteine)
- Iron-chelation (Deferipone)
- Therapy targeting genes involved in genetic PD:
  - LRKK2
  - GBA

TREATMENT OF EARLY PD

- P2B001 (Low dose of ER Pramipexole and Rasagiline)
- Exercise (Heterogeneous interventions > importance of dose, intensity and duration)

TREATMENT OF ADVANCED PD

- New extended-release versions of carbidopa/levodopa: IPX 203
- New A2A Inhibitors
- New anti dyskinesia medications (IR/IR Amantadine; JM-010; Mesdopetam (D3 antag); AV 101 (L4 chlorokynurenine/inhibits glycine co-agonist site of NMDA receptors), NLX-112 (5HT1A ago), Dipraglurant (negative allosteric modulator of mGlu5 receptor)
- New pumps for PD: Subcutaneous CD/LD (Neuroderm); Subcutaneous fCD/fLD (ABBV-951)
- Gene therapy: NN1b-1817 (AAV2 gene therapy encoding L-AADC, 3 doses)
- Adaptive close loop DBS
- Unilateral Focused ultrasound subthalamotomy for PD: Not enough data
- Stem cell therapy for neurorestoration

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

Thank you