ADVANCES IN PARKINSON DISEASE TREATMENT AND THE IMPORTANCE OF EXERCISE

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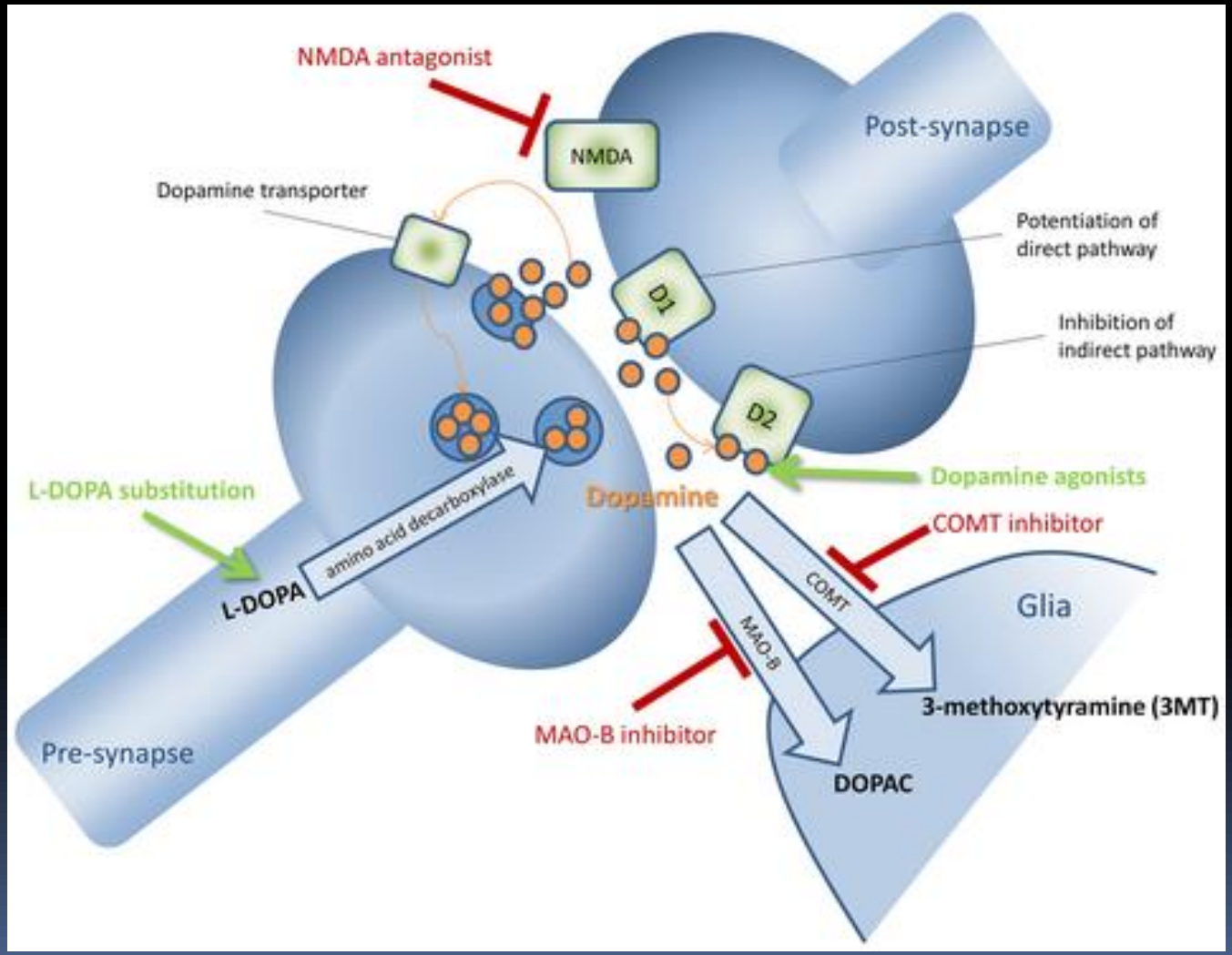
InMotion

PD motor symptoms: Therapeutic targets



Oertel W, Shulz JB. J Neurochem 2016

Modest symptomatic benefit

- MAO-B inhibitors (selegiline, rasagiline, safinamide)
  - **Not proven to be neuroprotective**
  - Modest benefit
  - Used for motor fluctuations (extends half life LD)
- Anticholinergics
  - May help tremor rigidity, not bradykinesia
  - Many side effects
  - Largely reserved for young subjects
- Amantadine
  - Mild improvement for PD symptoms, often transient
  - Most used for treatment of dyskinesia
  - affects dopamine, acetylcholine and glutamate
  - **Renal clearance (care with elderly or kidney disease)**

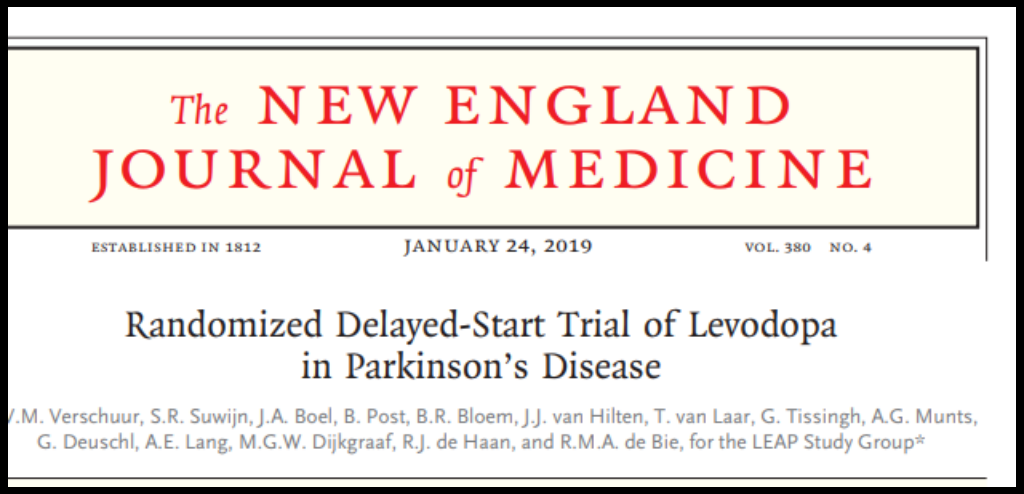
Robust symptomatic treatment: Levodopa

- Gold standard for > 50 years
- Efficacious as monotherapy treatment for PD symptoms
- No evidence for enhanced disease progression

HIGH LIGHT

"Levodopa phobia": A new iatrogenic cause of disability in Parkinson disease

Roger Kurlan, MD



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 24, 2019 VOL. 380 NO. 4

Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

V.M. Verschuur, S.R. Suwijn, J.A. Boel, B. Post, B.R. Bloem, J.J. van Hilten, T. van Laar, G. Tissingh, A.G. Munts, G. Deuschl, A.E. Lang, M.G.W. Dijkgraaf, R.J. de Haan, and R.M.A. de Bie, for the LEAP Study Group*

- 445 with PD diagnosis within 2 years
- Randomized:
  - Oral levodopa 100 tid for 80 weeks
  - Placebo tid for 40 weeks then levodopa 100 tid for 40 week
- No difference
  - Disease progression
  - Rate of levodopa related dyskinesia over 80 weeks
- Levodopa at start with no detrimental effects

Verschuur et al. NEJM 2019

Robust symptomatic treatment: Dopamine agonists

	Half Life in hours
Pramipexole (Mirapex®) Pramipexole ER	8 hours (tid) 12 hours (1ce day)
Ropinirole (Requip®) Ropinirole XL	6 hours (tid) 47 hours (1ce daily)
Rotigotine patch (Neupro®)	5 hours: terminal half life

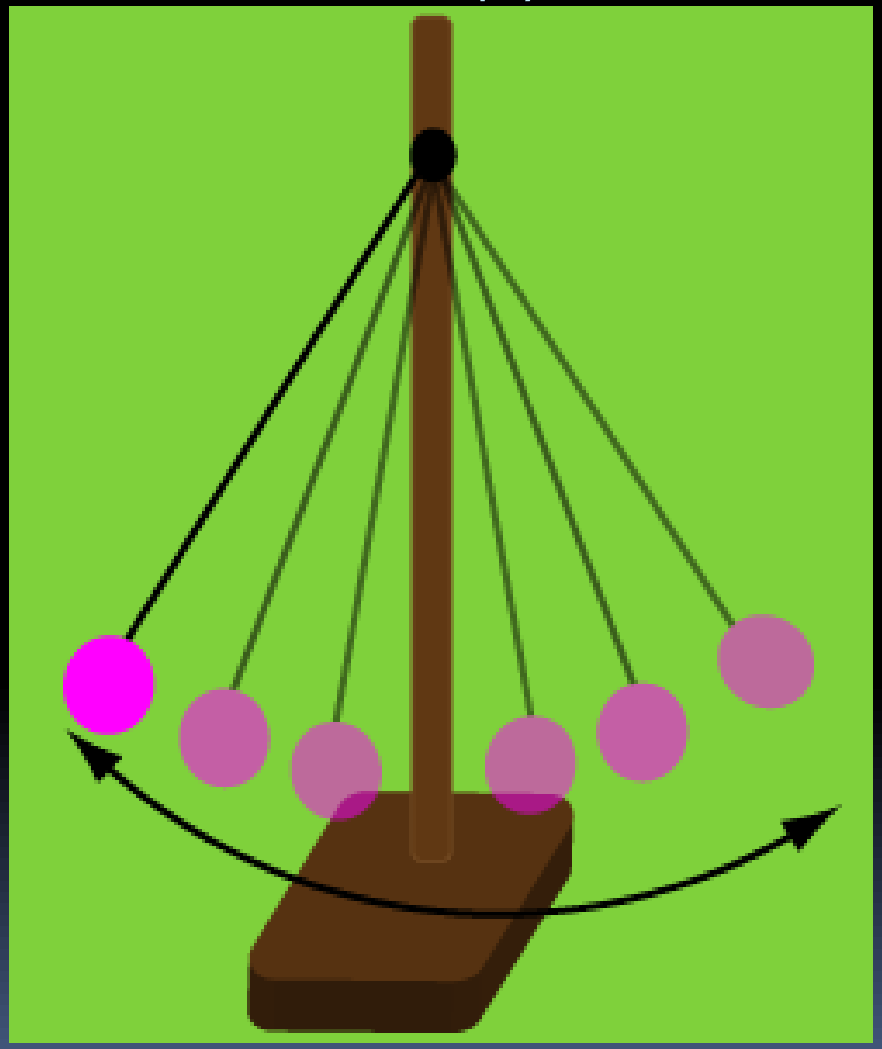
Initial treatment
levodopa vs dopamine agonists

- Levodopa
  - Better efficacy
  - Fewer side effects
  - No evidence for neurotoxicity
- Dopamine agonists
  - Less dyskinesia and motor fluctuations in the first 5 years with agonist; no difference at 10 years
  - Less benefit for PD severity
  - More side effects

Fox et al. Move disord 2018
Katzenschlager R et al Neurology 2008
Shannon K. Nat Clin Pract 2008

Initial monotherapy with dopamine agonists is not superior to initial monotherapy with levodopa

Levodopa



Dopamine agonists

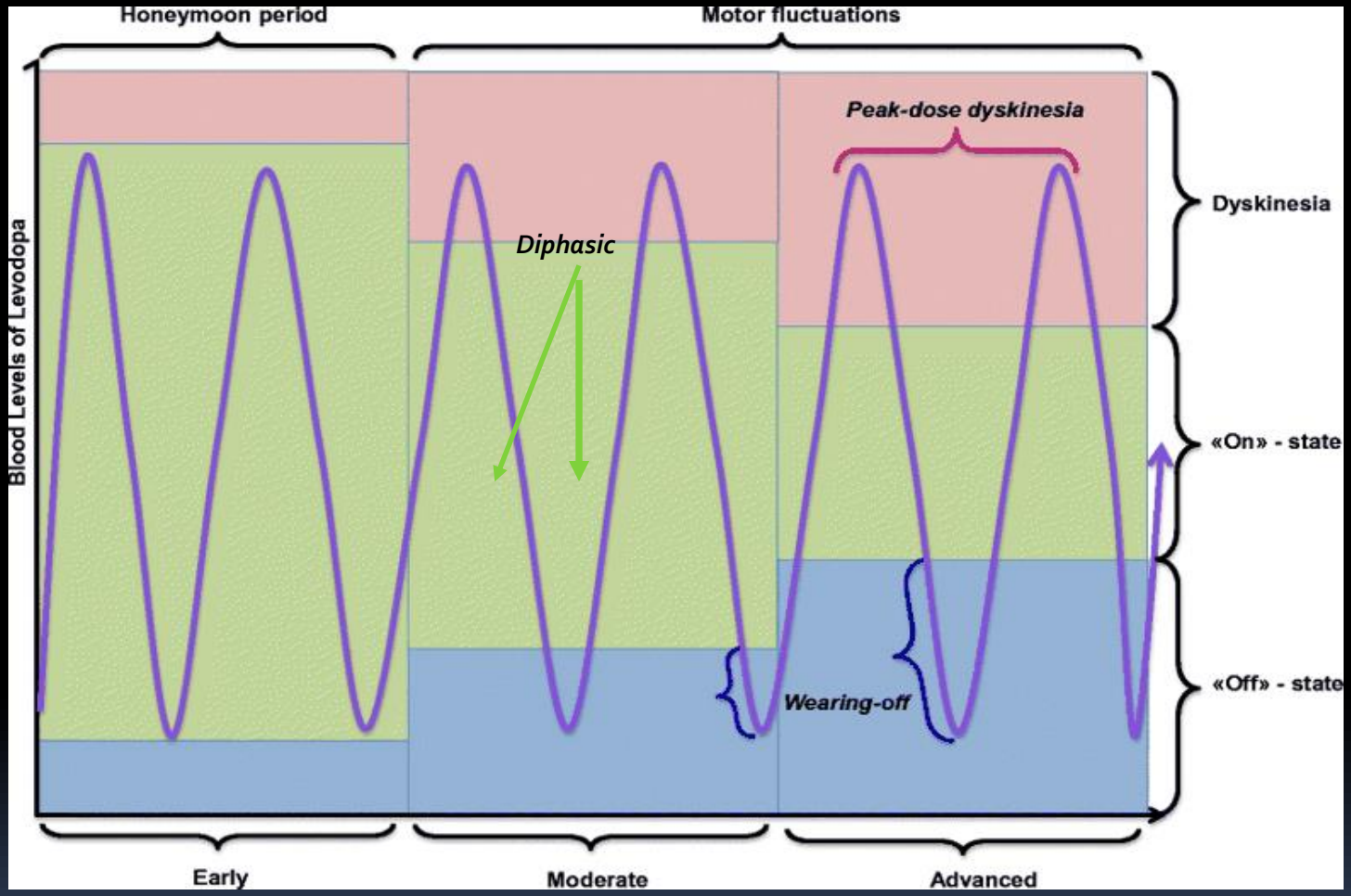
Oertel W, Schulz J. J Neurochem 2016

When to start levodopa

- At this time, no evidence that starting levodopa at PD diagnosis or delaying use of levodopa confers any benefit for motor complications
- Motor complications most prominently associated with disease duration and not levodopa treatment duration
- Most clinician experts use levodopa for symptomatic and functional reasons

Aradi S, Hauser R. Neurotherapeutics 2020

Motor complications in PD



Can we make symptomatic effect of levodopa last longer without causing troublesome dyskinesia

You et al. Cell and Tissue Res 2018

Available preparations of carbidopa/levodopa

Immediate release carbidopa/levodopa(Sinemet ®)

- Scored levodopa (Dhivy®)
- Orally dissolving (Parcopa®)

Slower release carbidopa levodopa

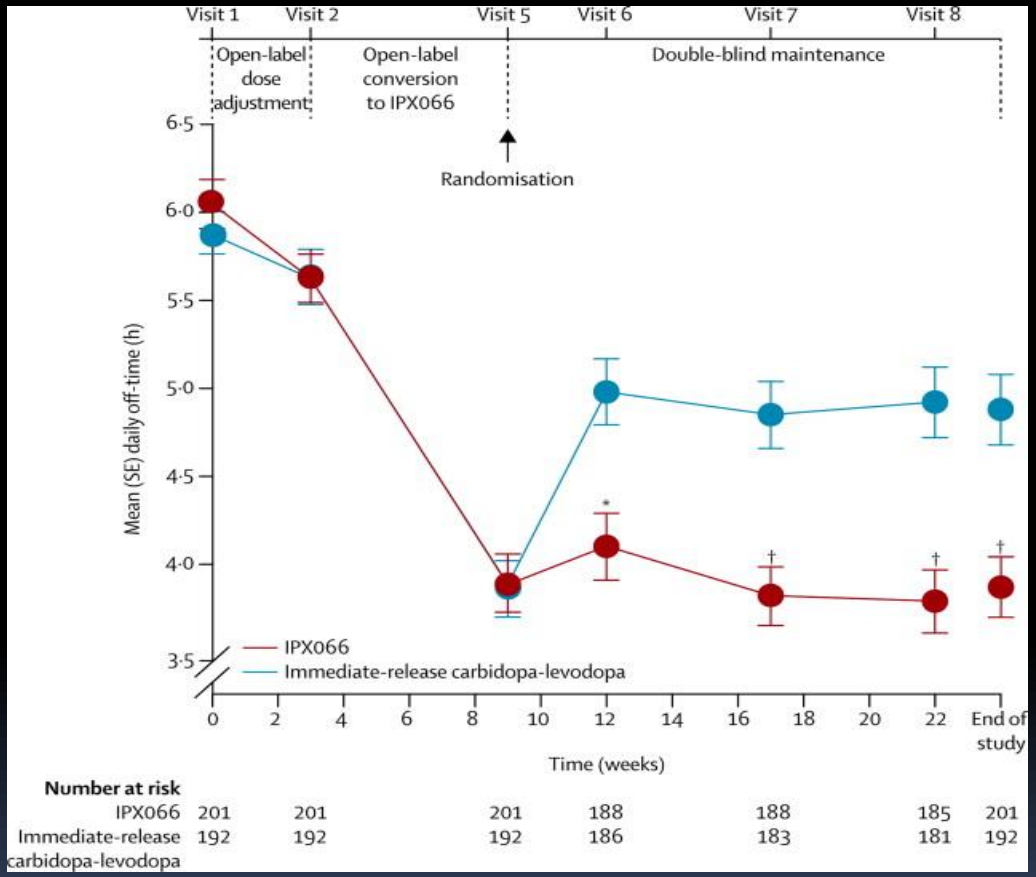
- Controlled release (Sinemet CR®)
- Combination LD/CD with entacapone (Stalevo®)
- IR/CR (Rytary®)
- Levodopa intestinal gel (Duopa ®)

Extended release levodopa (IPX066, Rytary®, Impax)

- Combines immediate release levodopa and extended release levodopa (2 types)
- Capsules containing beads of all formulations
- Rapid onset of action (IR) with extended effects from controlled release (ER)
- Doubles the duration of effect of regular levodopa
- Tartaric acid incipient to promote absorption of levodopa in the more alkaline gut.

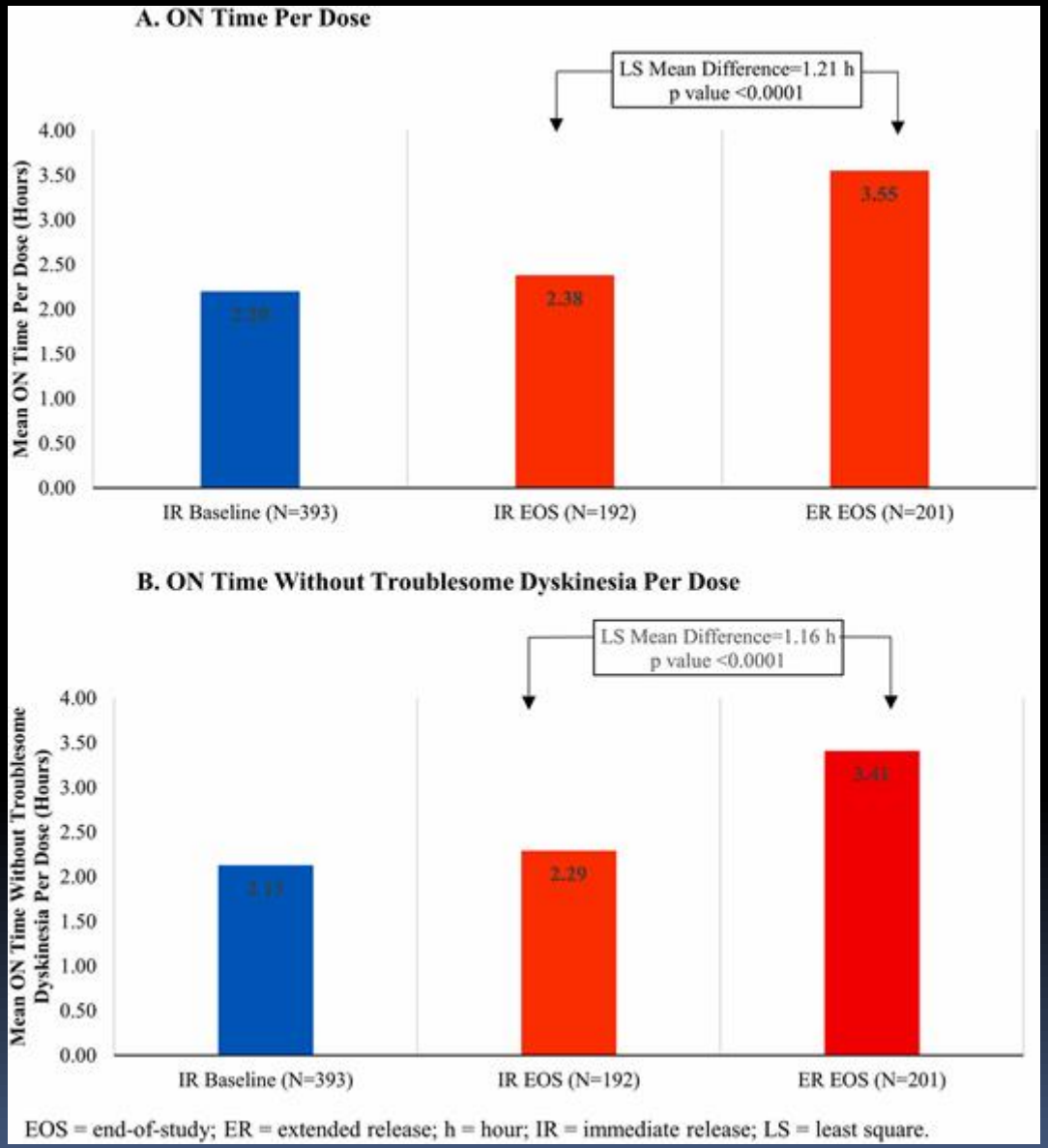
Margolesky and Singer. Adv Neurol Disord 2018

Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomized, double-blind trial



Caveat: Dose of levodopa was 45% higher in the IPX066 group

Hauser et al, 2015 Parkinsonism and related Disord



Hauser et al. Parkinsonism Rel Dis 2021

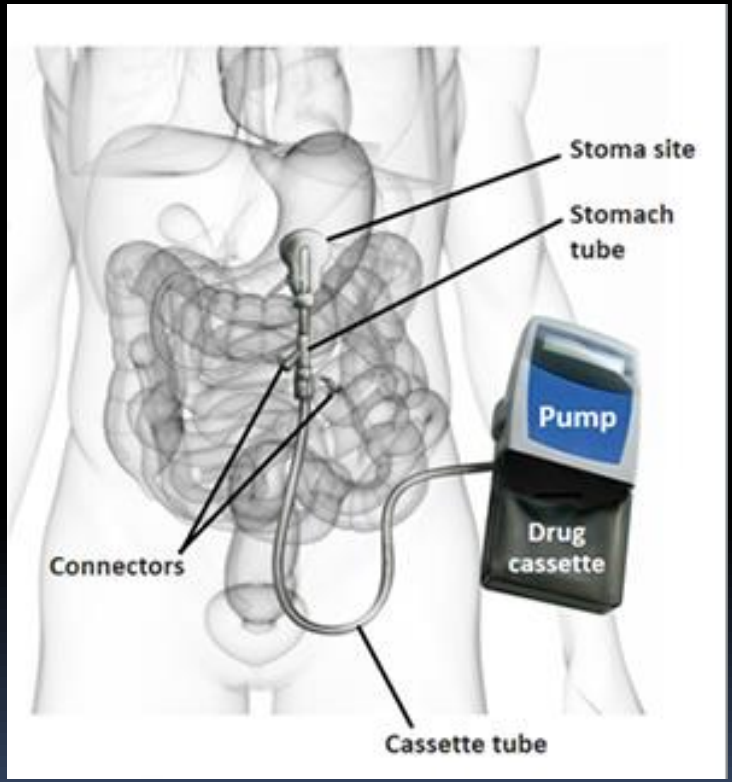
IPX203

- Reformulation of IPX066 (Rytary®)
- Longer acting (up to 7-8 hours)
- Phase 2 results positive
- Phase 3 study in 510 PD patients with motor fluctuations in progress

Modi et al. Clin Neuropharm 2019

Levodopa gel intrajejunal infusions Duopa ®

- Continuous release during the day
- Delivered directly to small intestine where levodopa absorbed
- No issues with slowed GI transit



Duopa® (levodopa gel)

- Long term meta-analysis: reduction of off time by 40-80%
- Approximately $60,000 per year
  - Coverage and reimbursement support
- Complications in up to 40%
  - device insertion
  - abdominal pain
  - nausea
  - post-operative wound infection
  - 40% levodopa associated peripheral neuropathy
    - increased homocysteine; reduced vitamin B12; increased methylmalonic acid; and reduced vitamin B6.

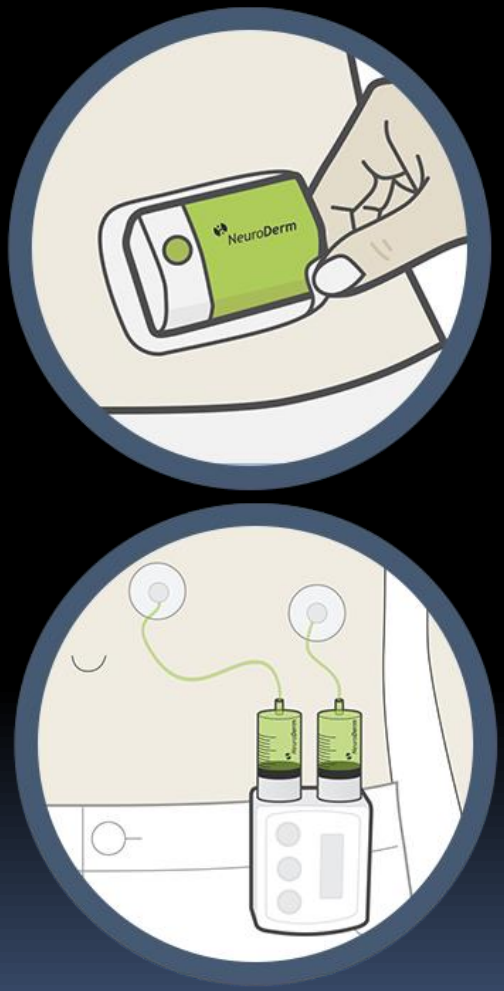
Fernandez et al. Mov Disord 2015

Romagnolo et al. Mov Dis Clin Prac 2018

Antonini A et al. Adv Ther 2021

In the pipeline: ND0612

- Continuous subcutaneous infusion of levodopa/carbidopa
- Stable plasma levodopa levels
- Reduction in off time without troublesome dyskinesia
- Limited by dosing of levodopa (900 mg per day)
- Subcutaneous levodopa



Giladi et al. Mov Disord 2015 (abstract)
Kieburtz et al. Mov Disord 2016
Olanow, Stocchi Mov Disord 2017

Extension study subcutaneous levodopa (ND0612)

- 2 treatments group (n=38)
  - Around the clock administration
  - 14 hour waking day with am levodopa tablet
- On and off time assessed at day 28

- Off time: reduction of 2 hours, greater in the 24 hour group
- On time without troublesome dyskinesia: increased by 3 hours
- Complete resolution in 8 with 24 hour infusion
- Improved dyskinesia
- AE: (N=4) abscess (1), infusion site reactions (nodules bruising) worsening PD

Olanow et al. J Parkinson disease 2021

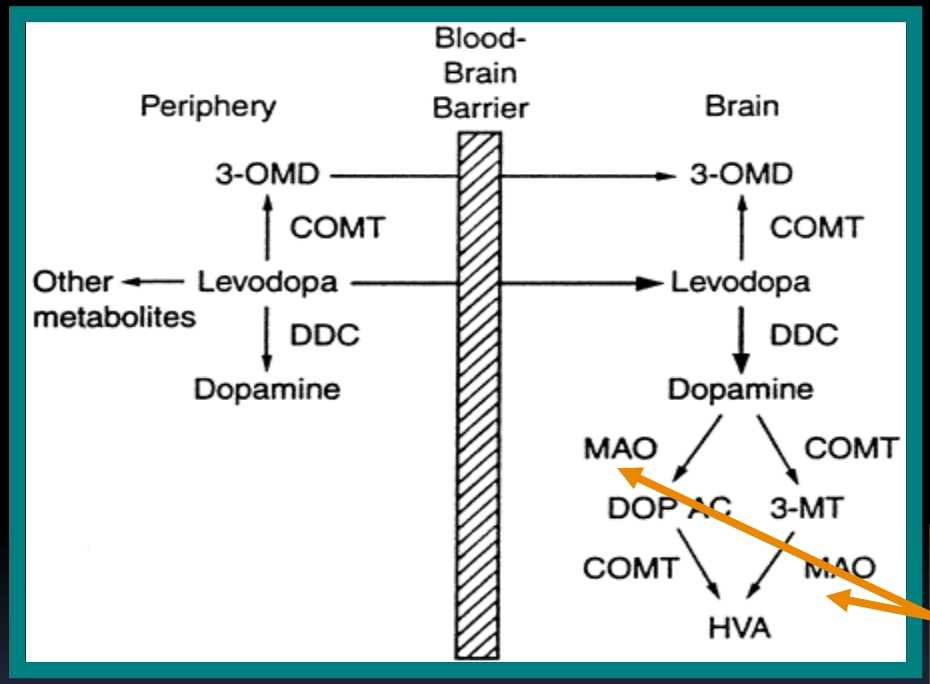
Prolong effect of levodopa

- COMT inhibition
- MAO B inhibition

- Provides 1-2 hours of increased time with effective treatment when combined with levodopa

Treatment of motor fluctuations

MAO-B inhibition

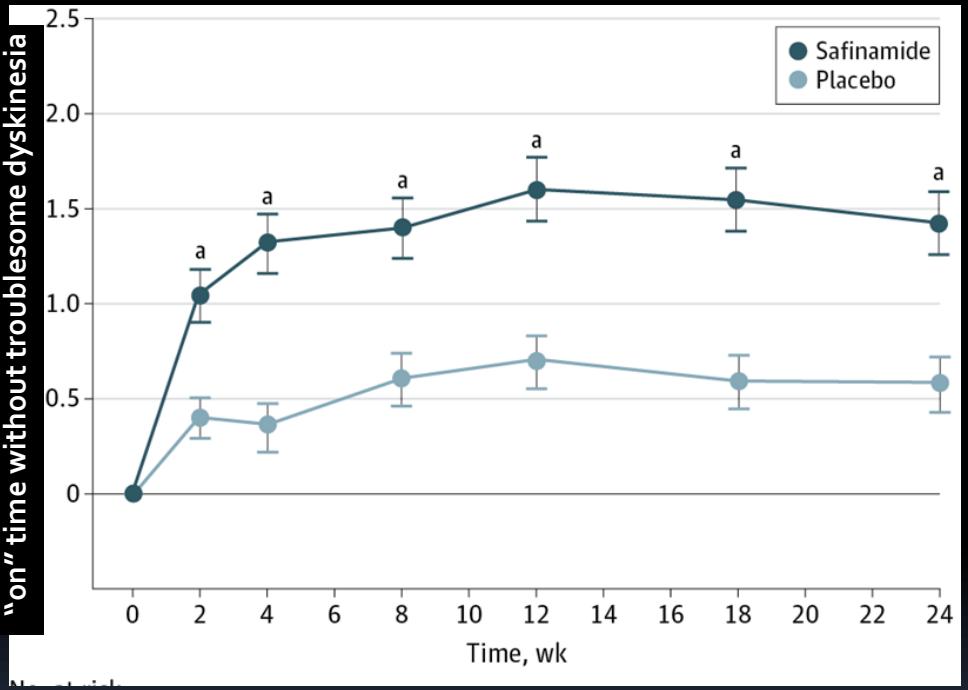


Fox et al. Move Disord 2018

Safinamide (Xadago®)
FDA approved 3/2017

- Potent, highly selective reversible MAO-B inhibitor
- Blocks voltage dependent Na and Ca channels
- Reduces neuronal glutamate release

- DB-PC-randomized
- 549 fluctuating PD
- Safinamide 100mg as tolerated
- Daily "on" time at 24 weeks increased by 0.8 hours
- Most frequent AE was modest increase in dyskinesia

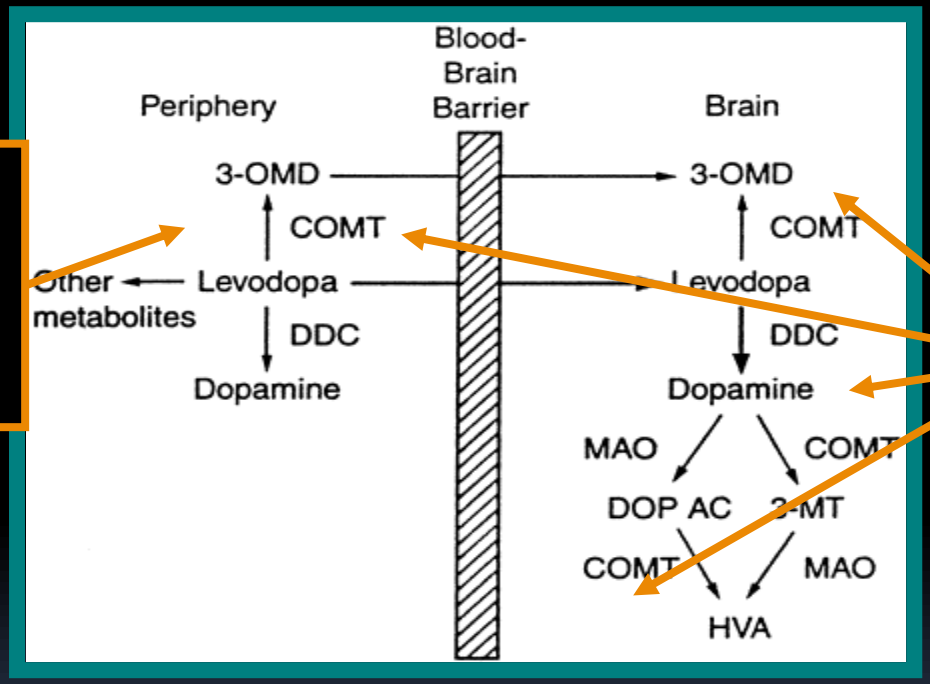


Schapira et al. JAMA neurol 2017

Treatment of motor fluctuations COMT inhibition

Entacapone
With every Idopa

Opicapone once daily



Tolcapone
Tid
Monitor for hepatotoxicity

Fox et al. Move Disord 2018

Opicapone: BiPark I and II

- FDA approved in 2020 as (Ontgentys®)
- Peripheral COMT inhibitor
- High potency, long duration
- Maintained effect at 1 year
- AE's mild, most frequent was dyskinesia

	placebo	Opicapone 25	Opicapone 50
N	135	125	147
% ≤ 1 hour off time	50.4	78 p=0.04	97 p=0.009
% ≥ 1 hour on time	45	63 p=0.004	62 p=0.006
Total increase in on time	59	104 p=0.02	111 p=0.005

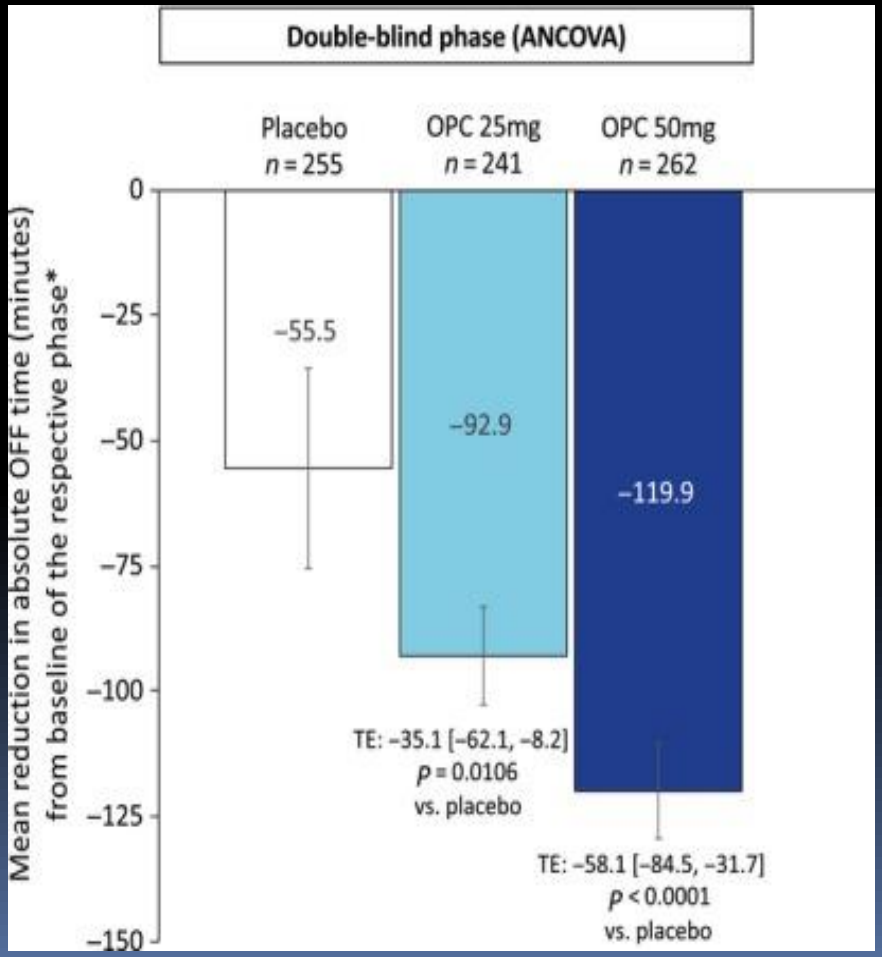
Lees et al. JAMA Neurology 2017

Opicapone: Long term efficacy Pooled analysis: BIPARK1 BIPARK2

- 633 fluctuating PD
- Opicapone 25, 50 mg qd
- Double blind with open label follow up for 1 year

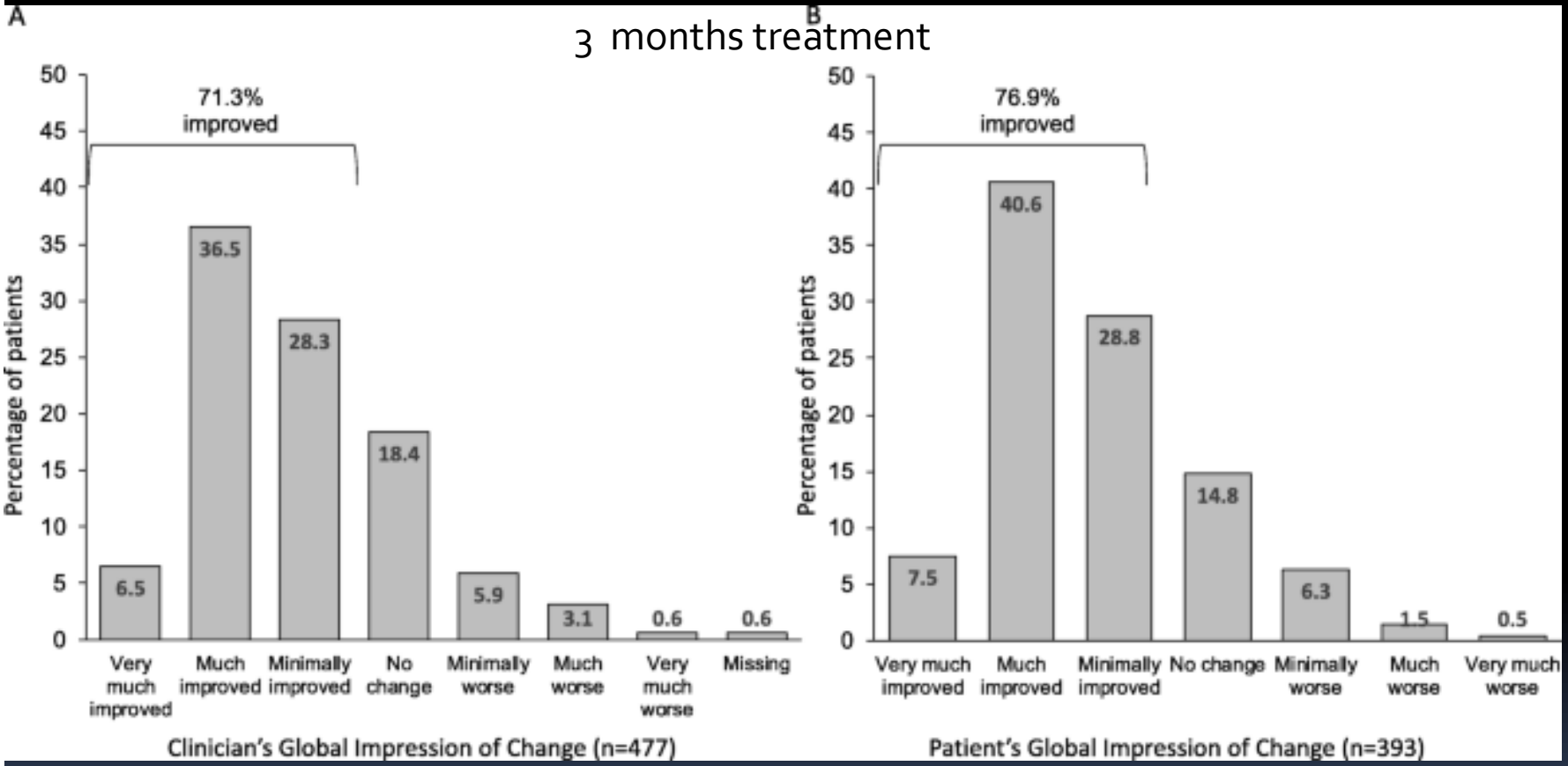
- Reduced off time, increased on time without troublesome dyskinesia

Ferreira et al. Eur J Neurol 2019



“Real World”: Optipark study

3 months treatment

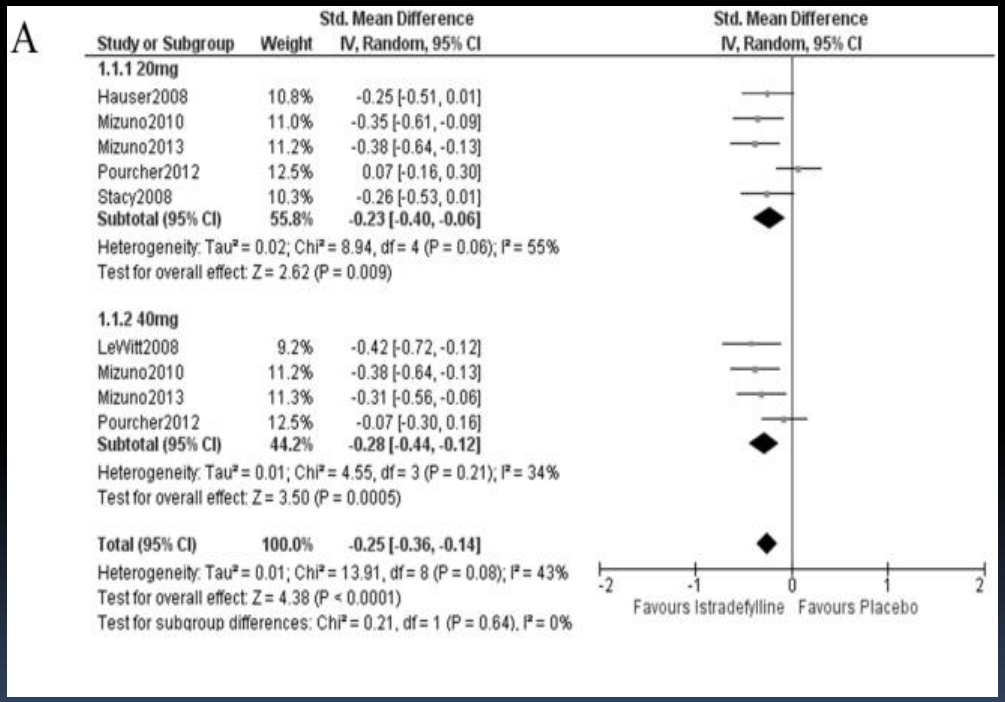


Open label, opicapone 50 qd, N= 393 fluctuating PD

Reichmann et al. Transl Neurology 2020

Istradefylline (Nourianz®)

- Adenosine A_{2A} receptor antagonist
- FDA approved as adjunct 2019 for "off" time in PD based on DBPC studies
- Variable results initially
- Approximately 1 hour less off time.
- Improved motor symptoms
- Dyskinesia most frequent AE



Sako et al. Sci Rep 2017

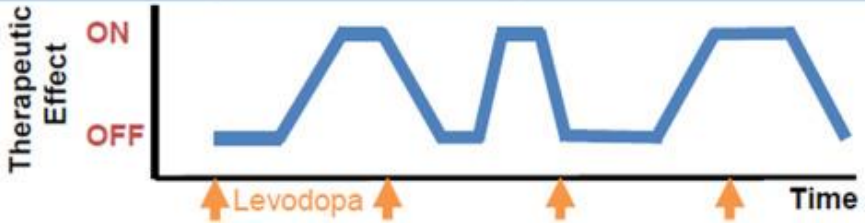
Istradefylline long term

- 308 fluctuating PD treated for 1 year
- Open label
- Istradefylline 20-40 mg/day

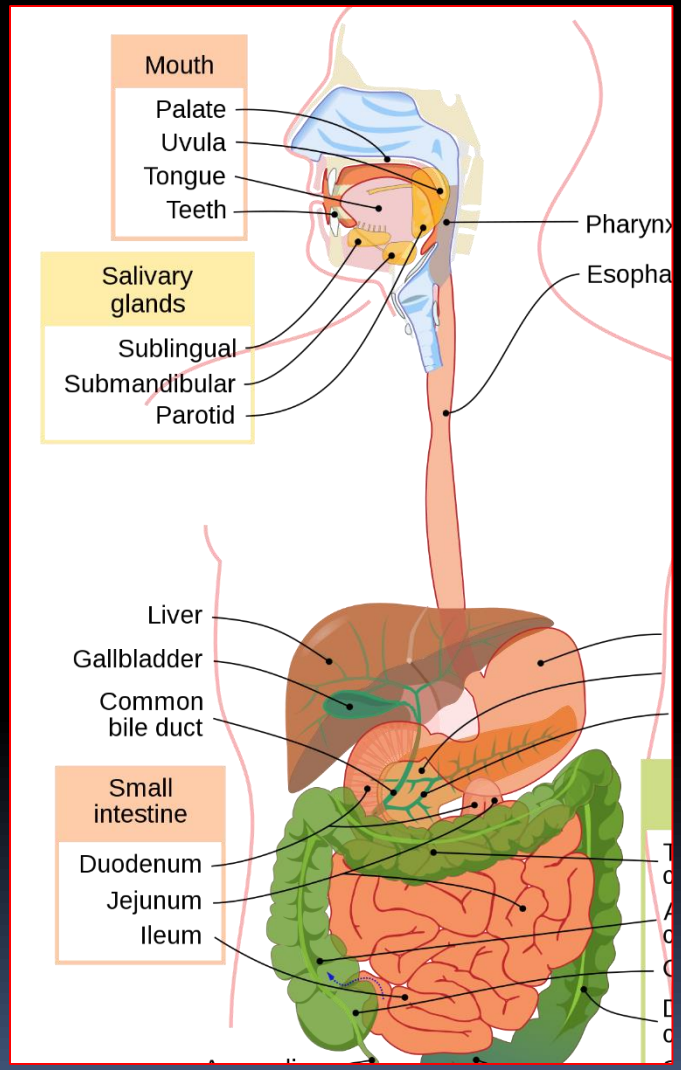
- Decrease in daily off up to 1 hour
- Most frequent side effect mild to moderate dyskinesia

Kondo et al. Clin Neuropharm 2015

Classification of levodopa-related motor fluctuations in PD

Clinical pattern	Mechanism	
Wearing-off	Levodopa – half-life Pre-synaptic storage	
Delayed-on	Gastric emptying Intestinal absorption	
Dose-failures (No-ON)	Gastric emptying Intestinal absorption Blood–brain barrier transport	
Random ON-OFF	Striatal Pharmacodynamic Changes	

Chaudhuri et al. Mov Disordr 2018


Mouth
Palate
Uvula
Tongue
Teeth
Salivary glands
Sublingual
Submandibular
Parotid
Pharynx
Esopha
Liver
Gallbladder
Common bile duct
Small intestine
Duodenum
Jejunum
Ileum

On demand therapies

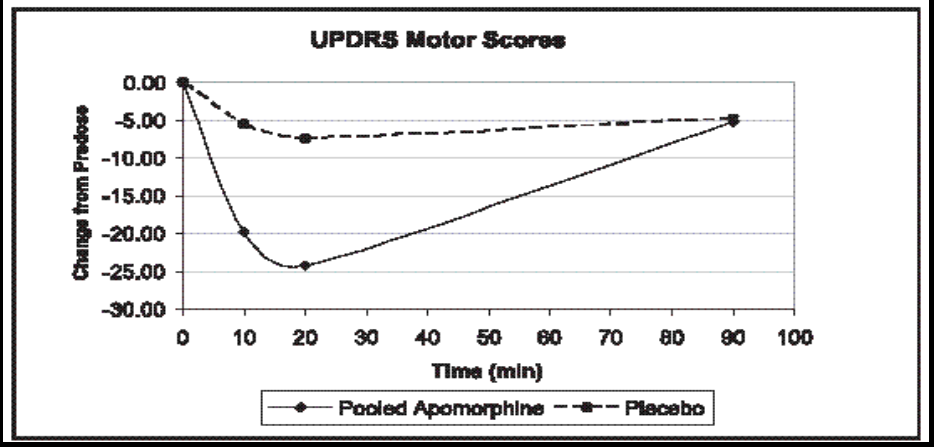
- Characteristics
  - By pass gastrointestinal system
  - Quick onset of action
  - Well tolerated
  - Easily administered

Hauser R et al. Post Grad Med 2021

Subcutaneous Apomorphine “rescue”

- Response equal to levodopa
- Sudden “off” periods
- Subcutaneous injection
  - onset 7.5-10 mins
  - duration 60-120m

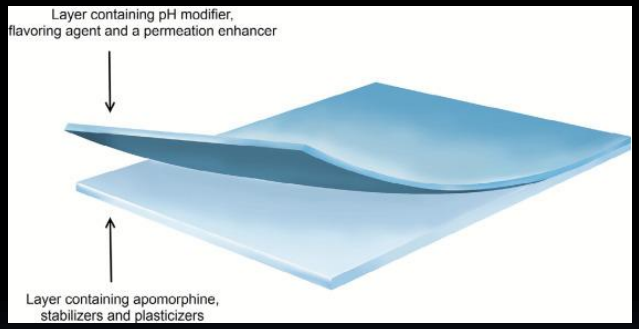
The figure below describes the mean change in UPDRS Motor Scores over time after pooled apomorphine and pooled placebo administration.



APOKYN™ Pen

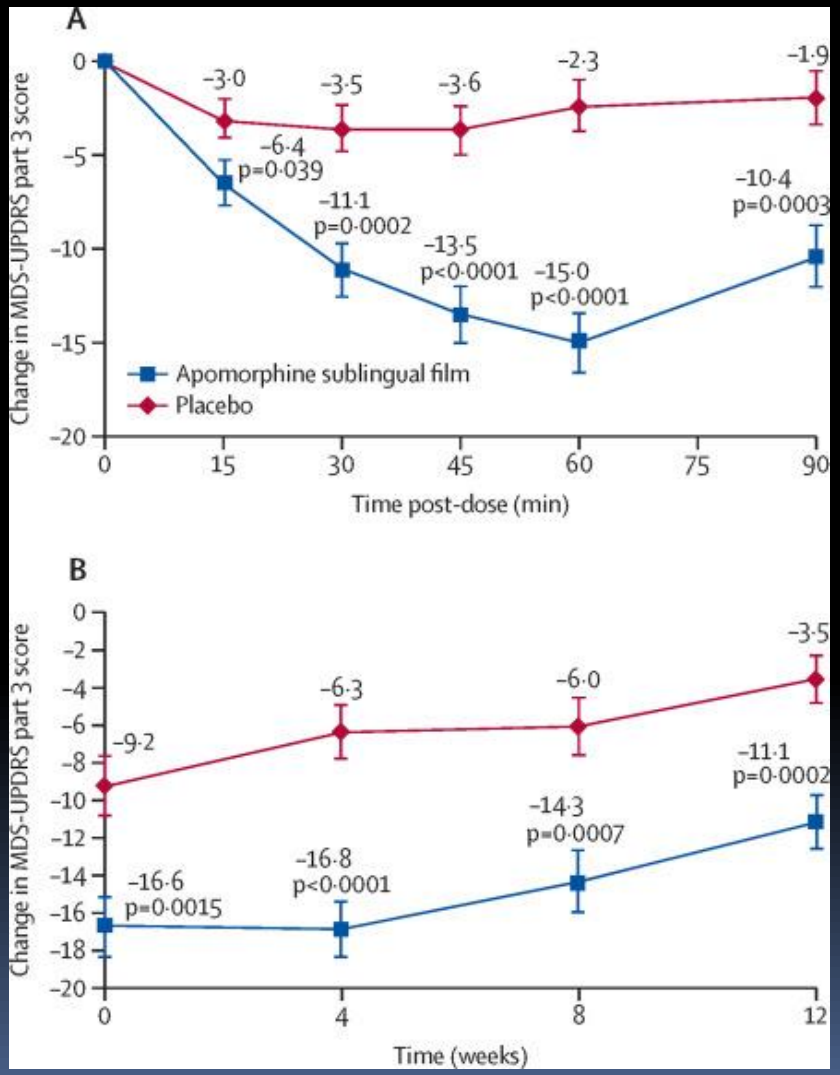
Sublingual Apomorphine FDA approved 2020 (Kynmobi®)

- Bi layer film
- Dissolves under the tongue into the circulation
- Avoids GI delays
- No first pass effect
- Available in multiple dose strengths



Sublingual Apomorphine

- DBPC study
- 109 PD with 2 hours off and morning off
- Maintained on usual regimen of PD meds
- Used from 10-35 mg depending on optimal dose



Olanow et al. Lancet Neurol 2020

Sublingual apomorphine

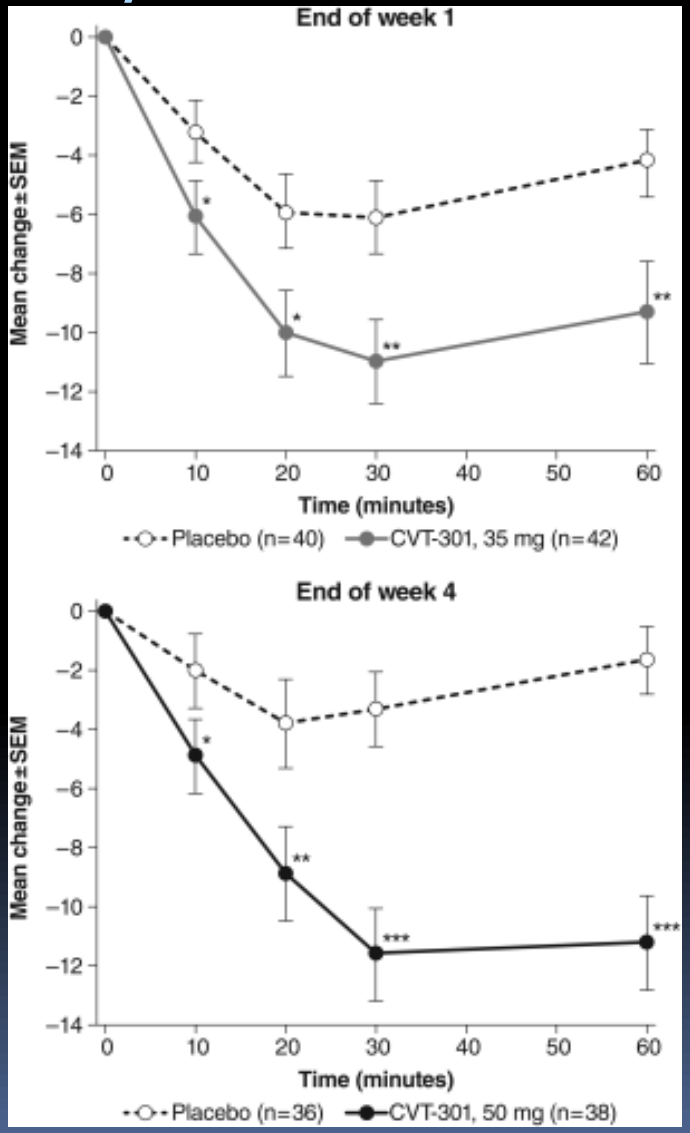
- Adverse effects
  - Oropharyngeal irritation (31%); discontinuation 17%)
  - Nausea
  - Somnolence
  - Orthostatic hypotension
  - Prolonged QT in 1 patient
  - ? Dyskinesia (not in this study)
- Special considerations
  - Pretreat trimethobenzamide 3 days
  - Drink water before
  - Keep under tongue until dissolved
  - Maximal 5 doses per day
  - Contraindicated with 5HT3 antagonists (ondansetron, etc.)

Olanow et al. Lancet Neurol 2020
Package insert

Inhalational Levodopa :Inbrija® FDA approved 12/2018

- 4 week RCT
- 86 fluctuating PD subjects
- 2 doses per day
- UPDRS part III improved in 10 minutes
- 0.8 hours less off time daily
- PGIC improvement in 72% CVT vs 46% placebo
- No change in PFT's

- Approved for intermittent "off" periods in PD up to 5 per day

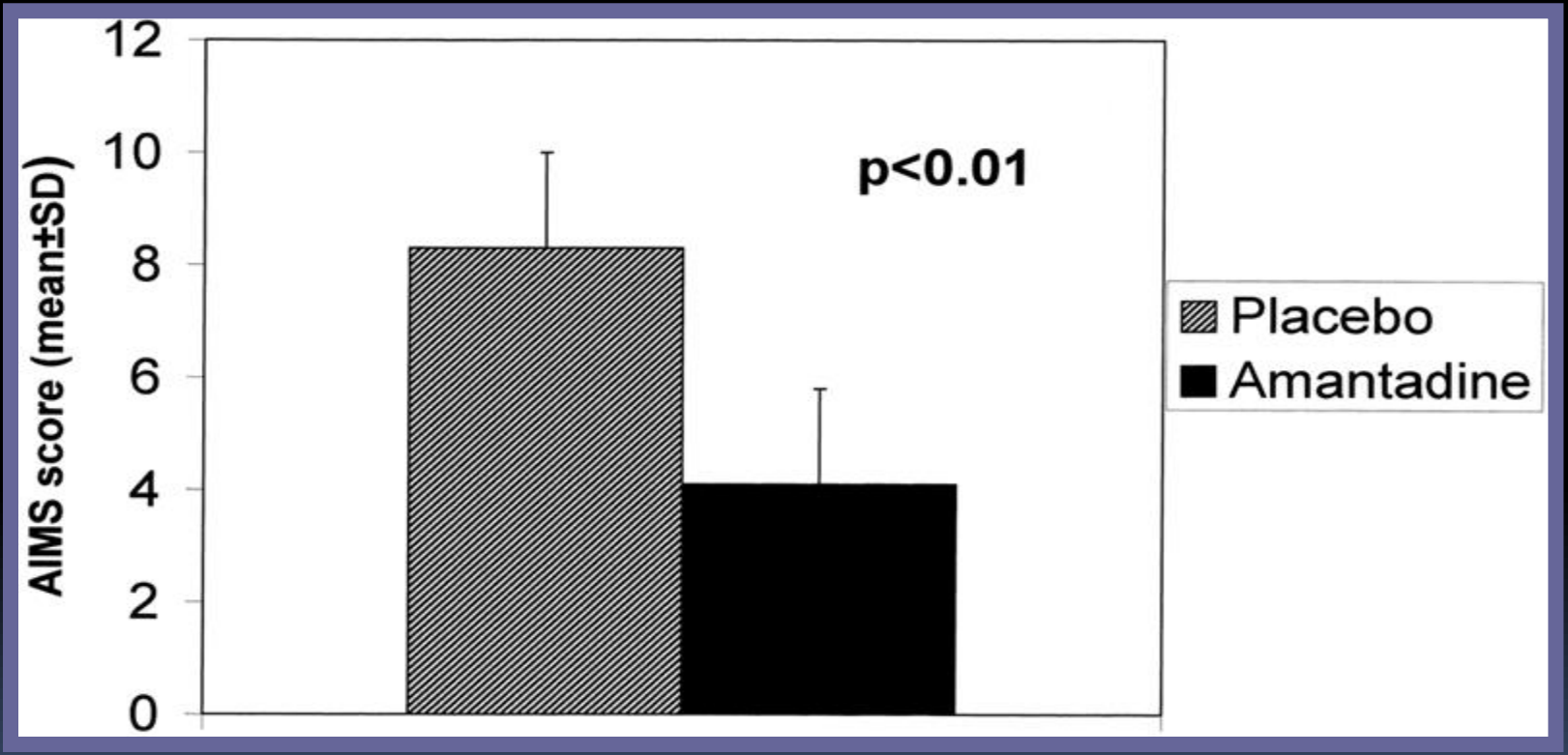


LeWitt et al. Move Disord 2016

UPDRS part III

Treatment of dyskinesia
Amantadine

mean dyskinesia score during placebo and amantadine IV infusions



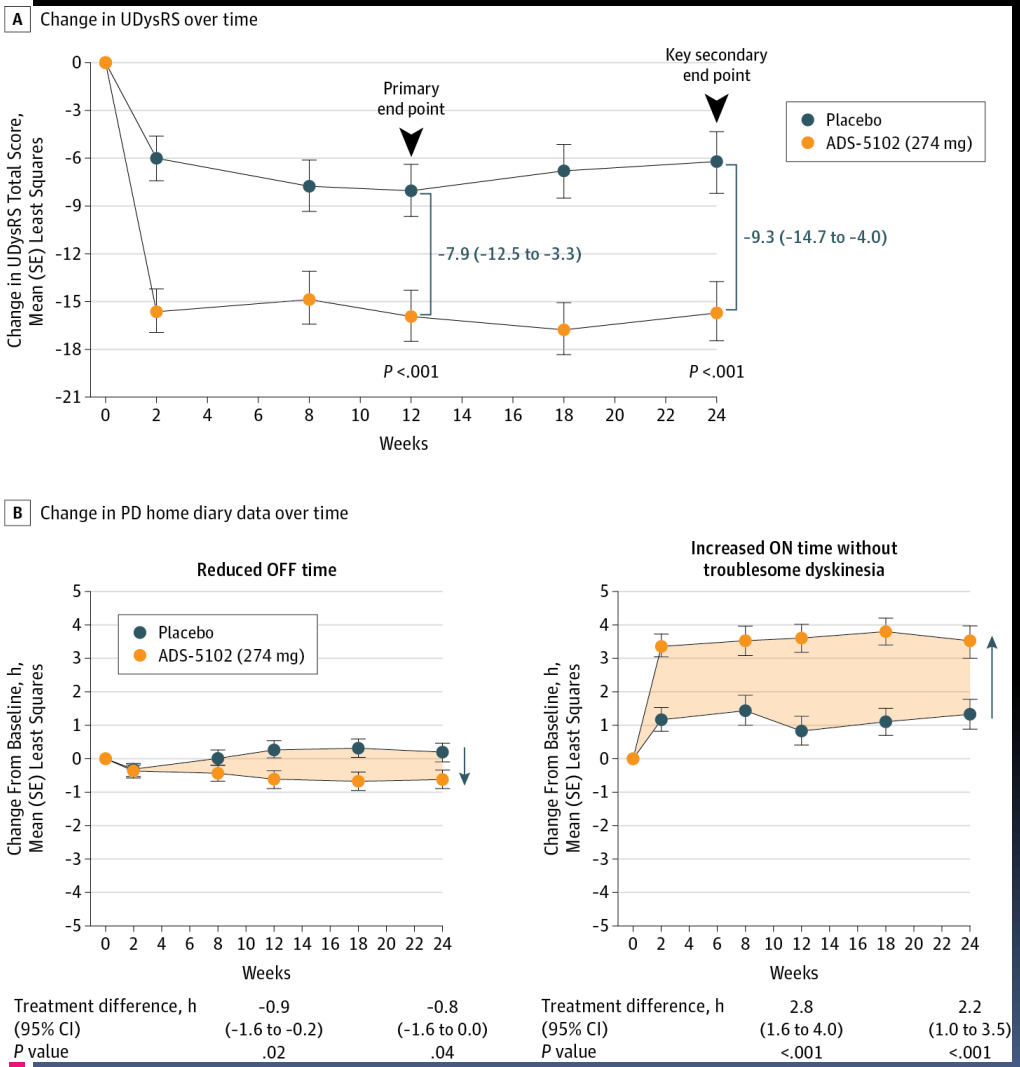
Del Dotto et al. Move Disord 2001;16:515.

ADS 5102 Amantadine Extended release (Gocovri®) EASE LID study
FDA approved August 2017 (Adamas Pharmaceutical)

- DBRPC study
  - 126 PD patients on levodopa randomized
    - 2 half hour "on"times with troublesome dyskinesia (peak dose)
  - ADS-5102 at 274 mg dosed at bedtime
  - Primary outcome 12 weeks
  - Study continued to 24 weeks
  - Primary and secondary outcome measures:
    - Δ baseline of Unified Dyskinesia Rating Scale (UDysRS)
    - Hauser diaries

Pahwa et al. JAMA Neurol 2017

Extended release amantadine



- Reduced dyskinesia
- Reduced off time (0.9 hours)
- Increased on time without troublesome dyskinesia (2.7 hours)
- Adverse effects with ADS-5102
  - Visual hallucinations (21%), peripheral edema (21%) , dizziness, dry mouth, constipation, livedo reticularis (9.5%)
  - No impulse control disorder
- EASE-LID 3 with similar results

Pahwa et al. JAMA Neurol 2017
Oertel et al. Mov Disord 2017
Hauser et al. Neurol Ther 2021

Extended Release Amantadine FDA approved 2021 for OFF episodes

- Pooled data from phase 3 trials (N=2)
- Improves dyskinesia
- Improves "on time" without /or with non troublesome dyskinesia by 4 hours vs placebo
- Reduce OFF time by 1 hour vs placebo
- Improves motor aspects of experiences of daily living
  - Freezing, tremor, getting out of bed,car,deep chair, eating tasks

Hauser et al. Neurol Ther 2021

Treatments currently being evaluated

Drug	Mechanism of Action	Clinical Trial Results
Glutamate receptor antagonists and modulators		
Gocovri (extended-release amantadine)	Non-competitive antagonist at glutamate NMDA receptor	Significant reduction in UDysRS scores, increase in ON time without troublesome dyskinesia and decrease in OFF time, from EASE LID (NCT02136914) and EASE LID 3 (NCT02274766) trials.
Dipraglurant	Negative allosteric modulator of mGlu5 receptor	Phase II randomized, double-blind, placebo-controlled study (NCT01336088) showed safety and tolerability and antidyskinetic efficacy.
Foliglurax	Positive allosteric modulator of mGlu4 receptor	Phase IIa randomized, double-blind, placebo-controlled study (NCT03162874) failed in showing efficacy on LID.
L-4-chlorokynurenine	Inhibition of glutamate NMDA receptor activation (selective antagonism of glycine's modulatory binding site)	Phase II randomized, double-blind, placebo-controlled, crossover proof-of-concept study (NCT04147949) will test efficacy on LID.
Naftazone	Glutamate release inhibitor	Phase II randomized, double-blind, placebo-controlled crossover study (NCT02641054) did not show efficacy on LID.
Serotonin receptor agonists		
Eltoprazine	Serotonin 5-HT1A/B receptor agonist	Phase I/IIa study proved safety, tolerability and antidyskinetic properties of 5 mg eltoprazine. Multicenter phase II, randomized, double-blind, placebo-controlled crossover dose-finding study (NCT02439125) has no posted results yet.
Buspirone	Serotonin 5-HT1A receptor agonist, D2 receptor antagonist, alpha-1 receptor agonist	Phase I randomized, placebo-controlled, double-blind study (NCT02589340) is testing efficacy of combination therapy with buspirone and amantadine on LID.
JM-010	Serotonin 5-HT1A and 5-HT1B/D receptor agonist	Phase II randomized, double-blind, double dummy, placebo-controlled study (NCT03956979) is testing efficacy of two doses of JM-010 on LID.
5-hydroxytryptophan	Serotonin precursor	Phase IIa randomized, double-blind, placebo-controlled crossover study showed a significant improvement in LID as assessed by UDysRS and UPDRS part IV scores.
Drugs acting on other targets		
Mesdopetam	Dopamine D3 receptor antagonist	Phase IIa study (NCT03368170) showed tolerability and reduction in LID severity. A phase IIb/III randomized, double-blind, placebo-controlled study (NCT04435431) is investigating Mesdopetam efficacy in 140 patients.
Pridopidine	σ1 receptor agonist	Phase II randomized, double-blind, placebo-controlled study to assess efficacy, safety, and pharmacokinetics of pridopidine for LID (NCT03922711) with no results posted yet.
Zonisamide	Inhibition of voltage-gated sodium channels, T-type calcium channels, MAO-B and carbonic anhydrase. GABA receptor agonist	Randomized, phase IV, open-label pilot study investigating tolerability and efficacy in treating LID has currently passed its completion date and has not been recently updated (NCT03034538).
Continuous intracerebroventricular (ICV) dopamine administration		Proof-of-concept phase I/IIb study of continuous ICV A-dopamine administration, to assess safety and feasibility and a subsequent 2-month, phase IIb, single-blind, randomized crossover study to assess efficacy on LID (NCT04332276) is ongoing.

Fabbrini A, Guerra A. J Exp Parmacol 2021

Exercise

RESEARCH ARTICLE OPEN ACCESS

Long-term Effect of Regular Physical Activity and Exercise Habits in Patients With Early Parkinson Disease

Kazuto Tsukita, MD, Haruhi Sakamaki-Tsukita, MD, and Ryosuke Takahashi, MD, PhD

Neurology® 2022;98:e859-e871. doi:10.1212/WNL.0000000000013218

Correspondence
Dr. Tsukita
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Original Investigation

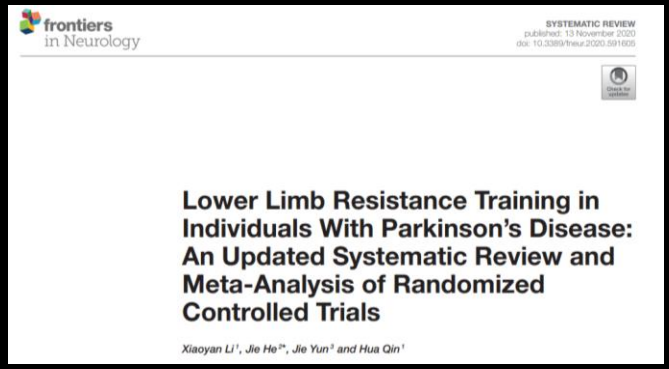
February 2018

Effect of High-Intensity Treadmill Exercise on Motor Symptoms in Patients With De Novo Parkinson Disease
A Phase 2 Randomized Clinical Trial

Margaret Schenkman, PhD, PT[1]; Charity G. Moore, PhD[2]; Wendy M. Kohrt, PhD[3,4]; Deborah A. Hall, MD, PhD[5]; Anthony Delitto, PhD, PT[6]; Cynthia L. Comella, MD[5]; Deborah A. Josbeno, PT, PhD[2]; Cory L. Christiansen, PhD, PT[1,4]; Brian D. Berman, MD, MS[7]; Benzi M. Kluger, MD[7]; Edward L. Melanson, PhD[4,8]; Samay Jain, MD[9]; Julie A. Robichaud, BS-PT, MHS, PhD[10]; Cynthia Poon, PhD[11]; Daniel M. Corcos, PhD[12]

Author Affiliations | Article Information

JAMA Neurol. 2018;75(2):219-226. doi:10.1001/jamaneurol.2017.3517



frontiers in Neurology

SYSTEMATIC REVIEW
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Lower Limb Resistance Training in Individuals With Parkinson's Disease: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials

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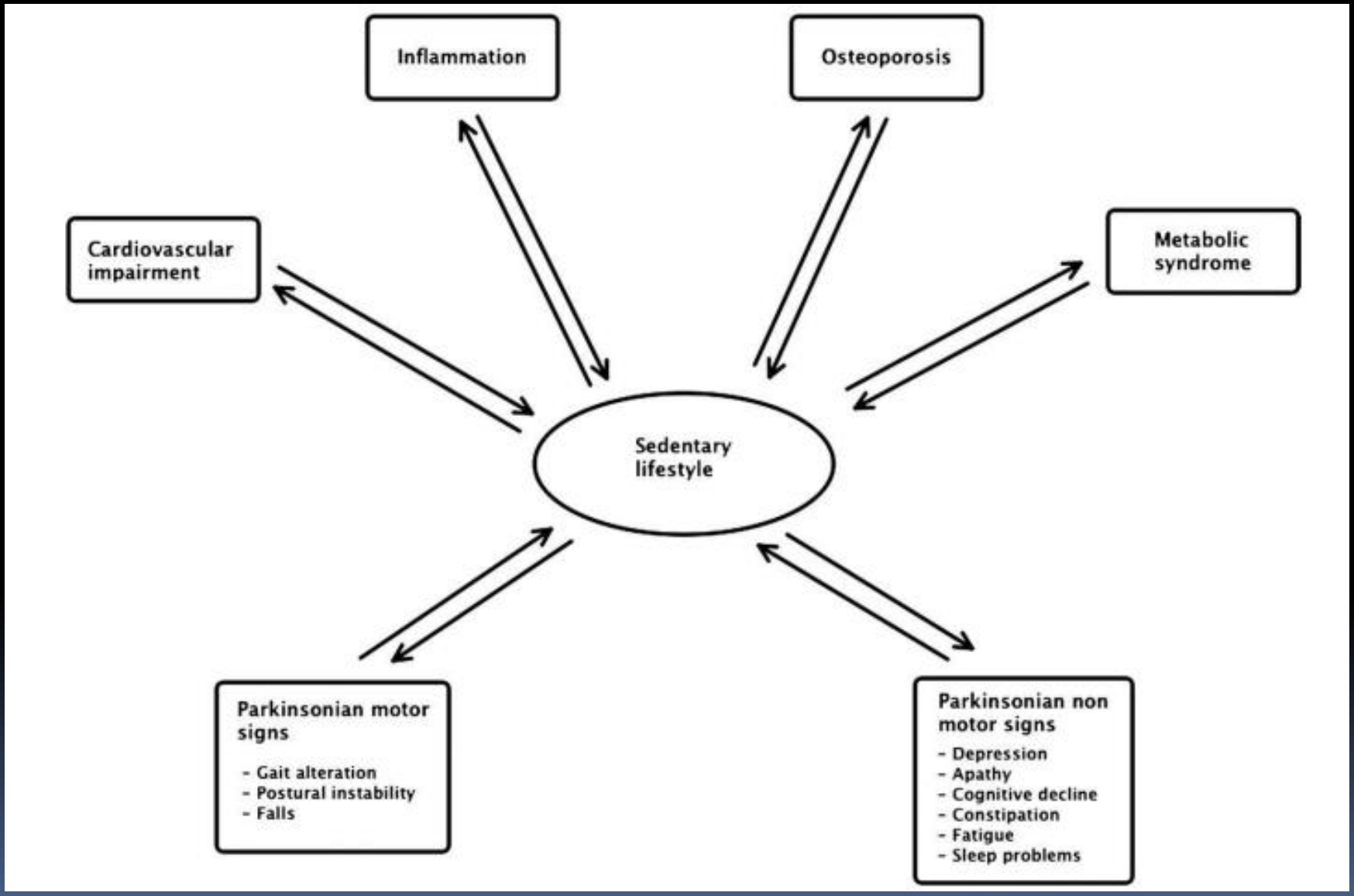
- Has potential for long-term benefits of exercise in individuals with PD
- Not known if exercise is truly neuroprotective and disease-modifying versus symptomatically but reversibly beneficial
- Rigorously designed, large-scale studies in progress

Crotty G and Schwarzschild M. Front Aging Neurosci 2020
Tsukitak et al Nueurology 2022
Schenkman et al. Jama Neurol 2018

The price of being sedentary



Frazzitta et al. Am J Phys Med Rehabil 2013

PD and exercise: many studies conducted

- LSVT BIG
- Treadmill
- Bicycle riding
- Yoga
- Boxing
- Dancing
- Walking
- Tai Chi

- Benefits
  - Reduces motor severity
  - Improves gait and balance
  - Reduces freezing
  - Reduces falls
  - Improves cognition
  - Improves overall fitness and flexibility

Exercise suggestions

- Check with your physician about your general health
- Most experts recommend 30-40 minutes a day and about 150 minutes a week.
  - Taking a minimum of 7,000 steps a day resulted in a 50% less risk of dying early.
- See a physical and/or occupational therapist
- Enroll in group exercise
- Do an enjoyable daily exercise, trying to push yourself a little harder than if you were doing the activity for leisure.
- Slowly increasing the pace or intensity should be encouraged.
- *JAMA Network Open*

Neurologist specialist

Medications

Education

Support

Research

Exercise