Diagnosis and Treatment of Motor Features of PD



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University of Toronto,
Toronto Western Hospital, UHN
Canada

ASPEN 2026

Videos; courtesy Toronto Western Hospital movement disorder clinic video library

Disclosures

- Research funding from NIH, Michael J Fox Foundation for Parkinson's Research, Parkinson Canada, Parkinson Foundation, Weston Foundation

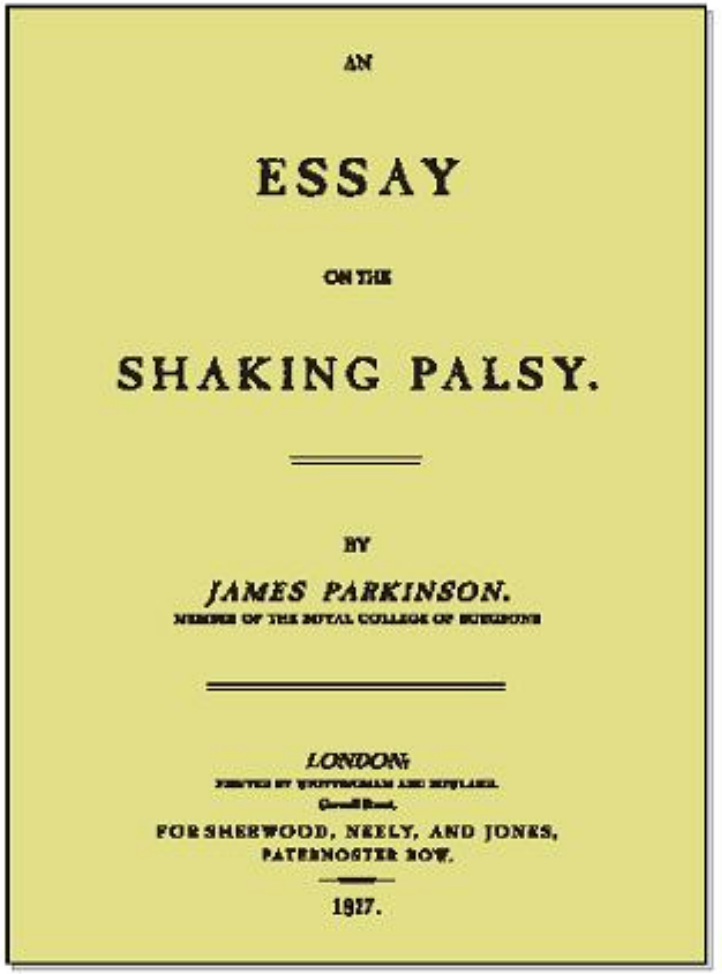
- Consultancy and funding from Abbvie, Lundbeck


INVISIBLE NON MOTOR SYMPTOMS
LOSS OF SMELL
SOFT VOICE
FACIAL MASKING
LEGO HANDS
REDUCED ARM SWING
TREMOR
SLOW MOVING
PAIN
STIFFNESS
RIGID
FREEZING
WWW.JONNYACHESONART.COM

Clinical diagnostic criteria for PD

- **Bradykinesia** and at least one of the following:
  - Rigidity
  - Rest tremor (4-6 Hz)
  - Postural instability

UK Brain bank criteria (1988)


AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON.

LONDON:

FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2]
Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17]
and Günther Deuschl, MD[18]

Movement Disorders, Vol. 30, No. 12, 2015

Clinically Established PD

- **Bradykinesia** (slowness and decrement in amplitude or speed)
  - And Rigidity
  - or Rest Tremor
  - or both
  - Plus: -
    - At least 2 supportive features
    - No absolute exclusion criteria
    - No Red Flags

Clinically Probable PD

- **Bradykinesia** (slowness and decrement in amplitude or speed)
  - And Rigidity
  - or Rest Tremor
  - or both
  - Plus: -
    - No absolute exclusion criteria
    - Allowing red flags as long as balanced by supportive features



npj | parkinson's disease

Article

Published in partnership with the Parkinson's Foundation

https://doi.org/10.1038/s41531-025-01206-6

Revisiting the 2015 MDS diagnostic criteria for Parkinson disease: insights from autopsy-confirmed cases

Check for updates

Susan H. Fox[1], Daniel G. Luca[2], Ronald B. Postuma[3,4], Roongroj Bhidayasiri[5,6], Francisco Cardoso[7], Gabor G. Kovacs[8,9,10,11,12], Regina Katzenschlager[13] & Claudia Trenkwalder[14,15]

npj Parkinson's Disease | (2025)11:360

- Scoping Review 1988 – 2025 for studies with sufficient Clinical data to apply MDS criteria in Pathological confirmed PD.
  - N = 28 studies;
  - Total Pathologically confirmed with clinical data PD n = 1526;
  - Total others (LBD/MSA/PSP/CBS) n = 1131

ISSUES:-

1. Lack of good clinical data that matches description of criteria
2. Co-pathology and impact on clinical phenotypes is not well described in any clinico-pathological series to date

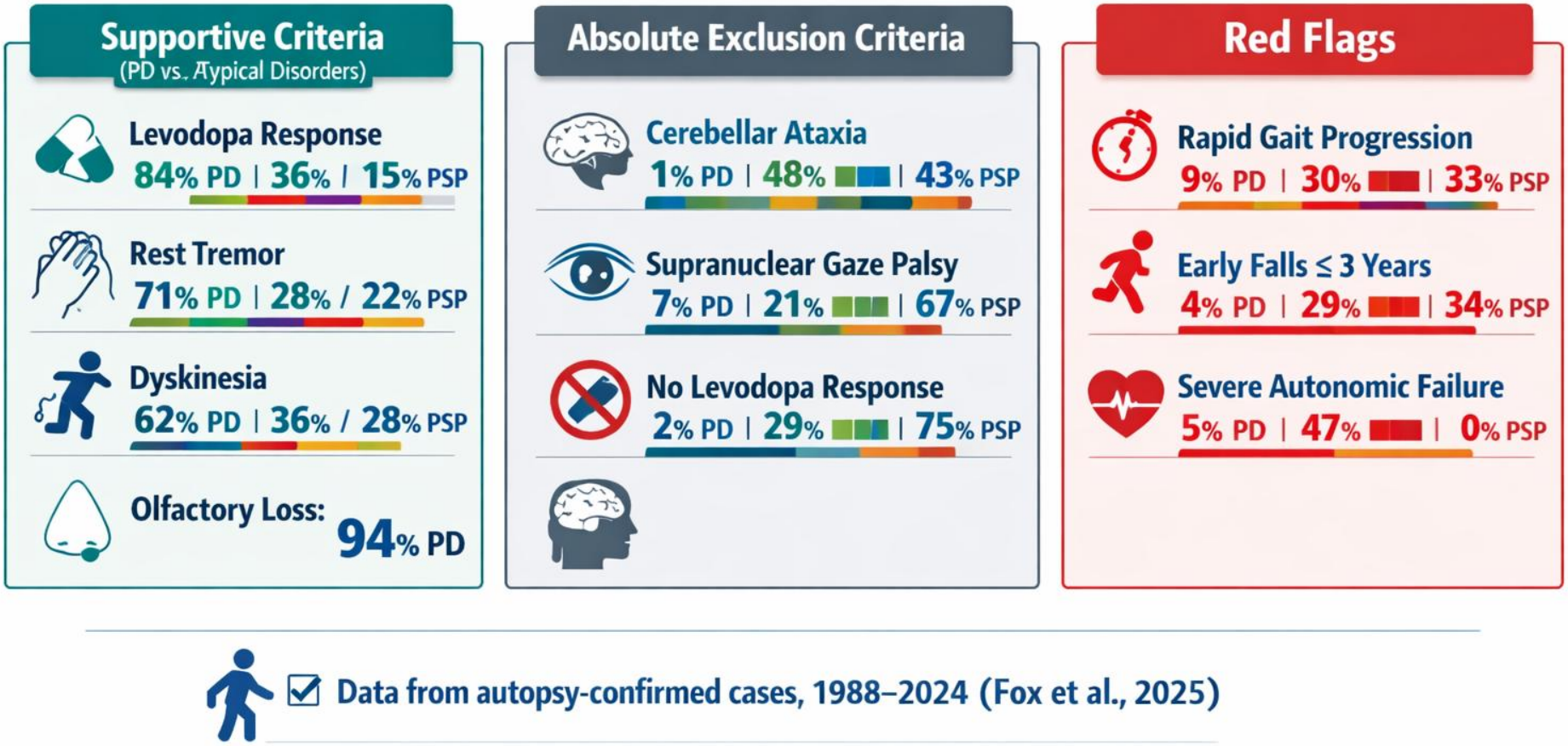


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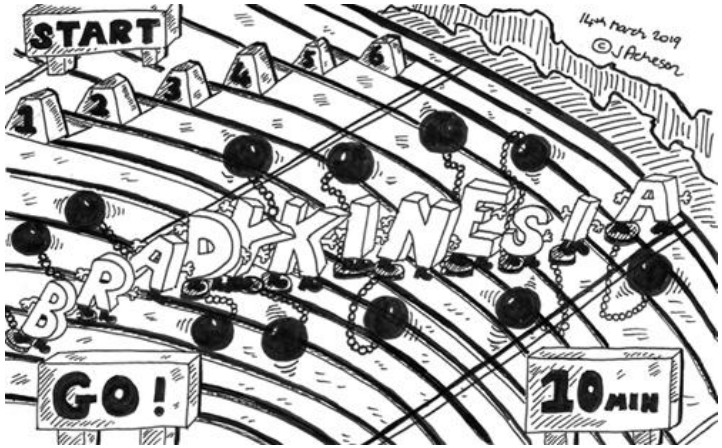
International Parkinson and *Movement* Disorder Society Parkinson and Lewy Body diseases

Clinical and Biological framework (MDS-CBF)

- Clinical Syndrome
- Biomarker
- Genetic characteristic
- Exposome

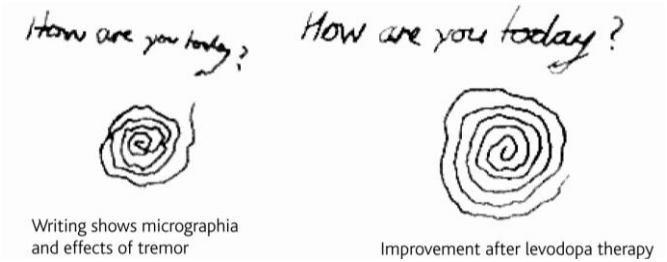
Bradykinesia

- Slowness of movement.
- Reduced amplitude of movement (fatiguing of repetitive movements).



Pictures from WPC Barcelona 2023; Artist: Jonny Acheson

- Hypomimia
- Decreased blinking
- Loss of spontaneous movements
- Micrographia
- Shorter steps
- Loss of automatic movements eg absent arm swing



Rigidity

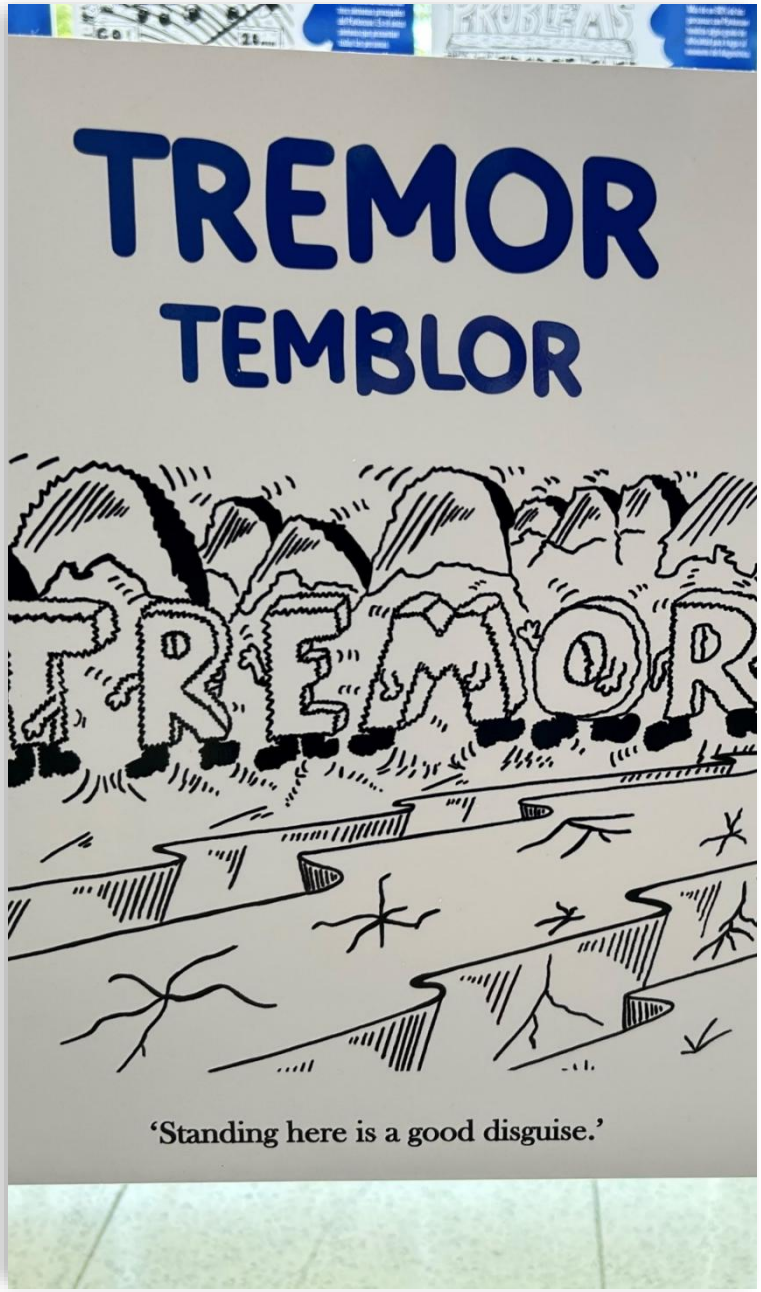


'Cogwheeling' 'ratchet' movements - co-existent tremor.

'Lead-pipe' resistance through all range of movement (vs spasticity = velocity dependent)

Tremor

- **Rest tremor**
- Slow frequency, 4-6Hz
- Fingers; thumb into palm = ‘pill rolling’
- Distal Arms commoner than legs
- Can affect Jaw
- Re-emergent tremor
  - 4-6Hz tremor that is seen after few seconds on outstretched hands or when walking
- Tremor associated with dystonia
- Postural and kinetic limb tremor



Parkinsonian Gait



- Slow
- Narrow base
- Reduced stride length
- Reduced/absent arm swing
- Hunched posture
- ‘Freezing’ on starting, turning, through narrow spaces
- ‘Festination’
- Poor balance

Postural deformities in PD

TABLE 1. Parkinson Disease (PD) and Associated Spinal Deformity

Postural Deformity	Definition	Prevalence in PD (%)
Sagittal plane deformity		
Camptocormia	Marked (minimum 45 degrees) flexion in the thoracolumbar spine laterally, almost complete resolution in the supine position	3-18
Antecollis	Marked (minimum 45 degrees) neck flexion, unable to fully extend the neck against gravity	5-6
Coronal plane deformity		
Pisa syndrome	Marked (minimum 15 degrees) lateral flexion that can be alleviated by passive mobilization or supine positioning	2
Scoliosis	Lateral flexion not relieved by voluntary or passive movement and lateral curvature of the spine of at least 10 degrees as measured by the Cobb method	9-91



Ha et al Neurosurgery 2015

Camptocormia

- Associations
  - Advanced disease
  - F > M
  - More motor disability
  - On higher daily dose of levodopa
  - Some response to stopping DA?

Box 2 Potential treatment modalities for treating camptocormia in Parkinson's disease

Non-pharmacological approaches
- Plaster corset
- Low-slung backpack with weight
- High-frame walker with forearm support
- Thoraco-pelvic anterior distraction orthosis
- Physiotherapies
  - Proprioceptive and tactile stimulation
  - Stretching
  - Postural re-education
  - Kinesiotaping on thoracolumbar paraspinal muscle

Pharmacological approaches
- Levodopa
- Botulinum neurotoxin injection
- Lidocaine injection

Surgical approaches
- Orthopaedic spinal surgical correction
- Unilateral pallidotomy
- Bilateral high-frequency deep brain stimulation
  - Subthalamic nucleus
  - Globus pallidus interna

Repetitive trans-spinal magnetic stimulation (immediate and short-lasting effect)

Camptocormia in Parkinson's disease: definition, epidemiology, pathogenesis and treatment modalities

Prachaya Srivanitchapoom and Mark Hallett

J Neurol Neurosurg Psychiatry 2015;**0**:1–11.

Expert Opinions on Treatments for PD

Parkinson's Disease 3

Medical, surgical, and physical treatments for Parkinson's disease

Tom Foltynie, Veronica Bruno, Susan Fox, Andrea A Kühn, Fiona Lindop, Andrew J Lees

Lancet 2024

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

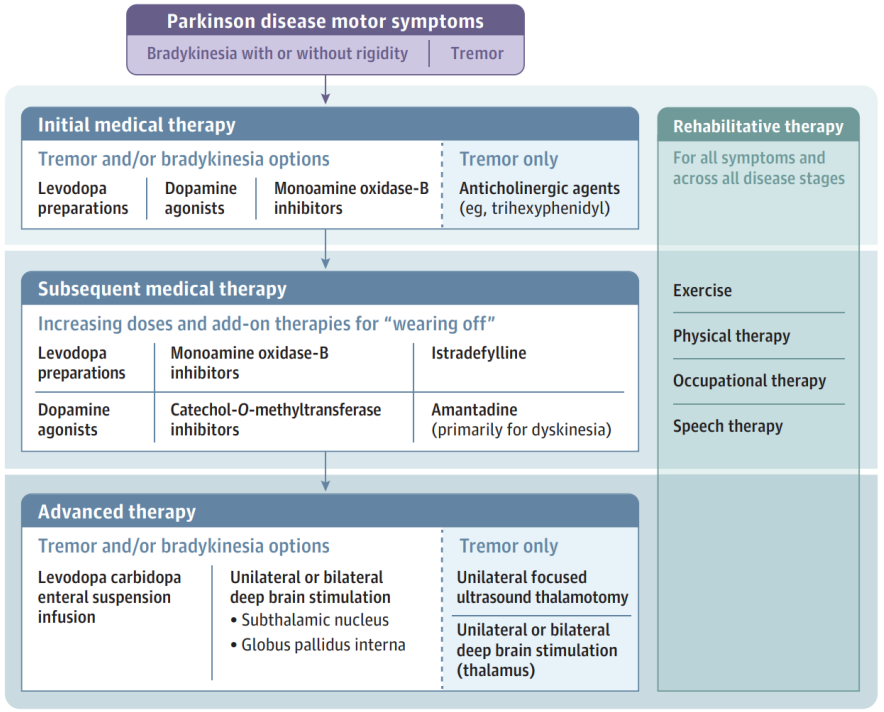
Allan H. Ropper, M.D., *Editor*

Parkinson's Disease

Caroline M. Tanner, M.D., Ph.D., and Jill L. Ostrem, M.D.

NEJM Aug 2024

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



JAMA | Review

Diagnosis and Treatment of Parkinson Disease
A Review

Melissa J. Armstrong, MD, MSc; Michael S. Okun, MD

JAMA February 11, 2020 Volume 323, Number 6

Evidence Based Medicine (EBM) Reviews of Treatments for PD











Future pharmacological therapies for PD?

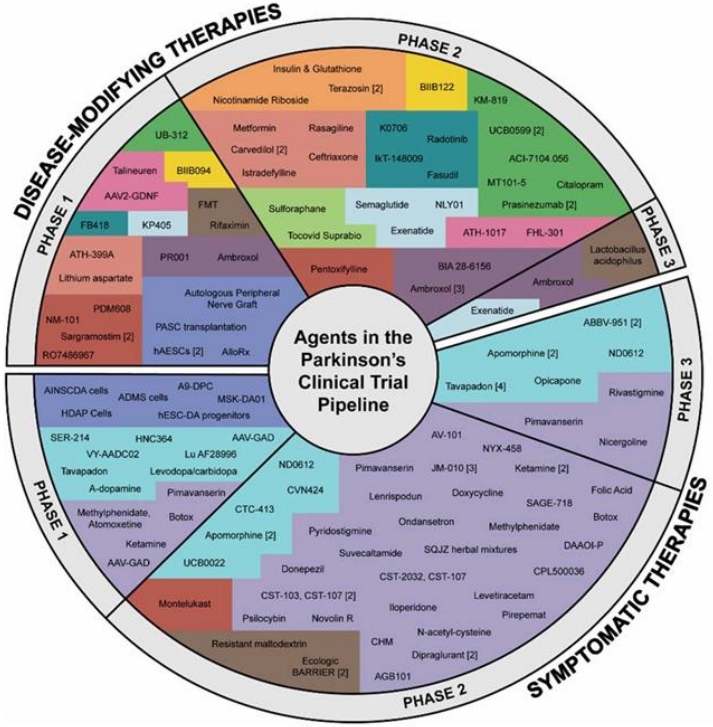


Fig. 2. A schematic of all of the agents in active clinical trials for PD, registered on ClinicalTrials.gov as of the January 31st, 2024 – 107 agents being tested in 136 trials. [#] after agent name indicates trial count, e.g., Apomorphine.[2] The pie graph is divided up according to the % of total trials, with ST Phase 1 : 14%, ST Phase 2 : 32%, ST Phase 3 : 10%, DMT Phase 1 : 16%, DMT Phase 2 : 26%, and DMT Phase 3 : 2%.

Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update

Kevin McFarthing[a], Sue Buft[b], Gary Rafaloff[c], Kenneth Pitzer[d], Brian Fiske[e], Anaya Navangul[f], Katelyn Beissert[f], Aleksandra Pilcicka[f], Rosie Fuest[g], Richard K. Wyse[f] and Simon R.W. Stott[f,*]

Active PD drug trials by phase and therapeutic novelty (as of January 31, 2024. ClinicalTrials.gov)

	Novel	Repurposed	Reformulation	New Claim	Total
Phase 1	18	8	14	1	**41**
Phase 2	29	40	6	4	**79**
Phase 3	4	4	6	2	**16**
Total	**51**	**52**	**26**	**7**	**136**
%	38%	38%	19%	5%	

Drugs
https://doi.org/10.1007/s40265-026-02327-9

REVIEW ARTICLE

Recent Developments in the Drug Treatment of Parkinson's Disease

Simon Leiter[1] · Philipp Mahlknecht[1] · Werner Poewe[1]

Received: 15 January 2026 / Accepted: 19 April 2026
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MDS-EBM
Symptomatic monotherapy

TABLE 2. Treatments for symptomatic monotherapy

Intervention	Drug	Efficacy conclusions	Safety[a]	Implications for clinical practice
Dopamine agonists	**Pramipexole IR**	Efficacious		Clinically useful
Nonergot	**Pramipexole ER**	Efficacious		Clinically useful
	Rotigotine	Efficacious		Clinically useful
	Piribedil	Efficacious		Clinically useful
	Ropinirole IR	Efficacious		Clinically useful
	Ropinirole PR	Likely efficacious		Possibly useful
Ergot	Cabergoline	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	DHEC	Efficacious		Clinically useful
	Pergolide	Efficacious		Clinically useful
	Bromocriptine	Likely efficacious		Possibly useful
Levodopa/peripheral decarboxylase inhibitor	**Standard (IR) formulation**	Efficacious		Clinically useful
	Controlled release (CR)	Efficacious		Clinically useful
	Extended release	*Efficacious*		*Clinically useful*
MAO-B inhibitors	**Selegiline**	Efficacious		Clinically useful
	Rasagiline	Efficacious		Clinically useful
Others	Anticholinergics	Likely efficacious		Clinically useful
	Amantadine	Likely efficacious		Possibly useful
Adenosine A_{2A} antagonist	**Istradefylline**	*Nonefficacious*		*Not Useful*

Any dopamine containing medication will reduce PD symptoms in early stages…

Factors affecting your choice

1. Benefit
2. Long term risk of developing fluctuations
3. Side effects
4. Cost

Levodopa is the best treatment for PD

- Most effective
- Sustained benefit
- Well tolerated
- Long track record

- **And its cheaper –**
  - *"Over 4 years, levodopa was associated with ....lower mean costs £5,083 (±287) vs £8,473 (±225) v dopamine agonist/MAOBI"*

Cost-Effectiveness of dopamine agonists and MAOB-I in Early PD. McIntosh E, et al PD MED Collaborative Group. Mov Disord. 2021 36:2136-2143.

Guidelines recommend Levodopa as first line therapy

Parkinson's disease in adults

NICE guideline
Published: 19 July 2017

NICE National Institute for Health and Care Excellence

Table 1 Potential benefits and harms of dopamine agonists, levodopa and MAO-B inhibitors

	Levodopa	Dopamine agonists	MAO-B inhibitors
Motor symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of daily living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

Abbreviation: MAO-B, monoamine oxidase B.

* Excessive sleepiness, hallucinations and impulse control disorders (see the summary of product characteristics for full information on individual medicines).

Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary

A Report of the AAN Guideline Subcommittee

Tamara Pringsheim, MD, Gregory S. Day, MD, MSc, Don B. Smith, MD, Alex Rae-Grant, MD, Nicole Licking, DO, Melissa J. Armstrong, MD, Rob M.A. de Bie, MD, PhD, Emmanuel Roze, MD, PhD, Janis M. Miyasaki, MD, Robert A. Hauser, MD, MBA, Alberto J. Espay, MD, Justin P. Martello, MD, Julie A. Gurwell, PhD, PA-C, Lori Billinghurst, MD, MSc, Kelly Sullivan, PhD, Michael S. Fitts, Nicholas Cothros, MD, PhD, Deborah A. Hall, MD, PhD, Miriam Rafferty, DPT, PhD, Lynn Hagerbrant, Tara Hastings, MA, Mary Dolan O'Brien, MLIS, Heather Silsbee, Gary Gronseth, MD, and Anthony E. Lang, MD, on behalf of the Guideline Subcommittee of the AAN

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Neurology® 2021;97:942-957. doi:10.1212/WNL.0000000000012868

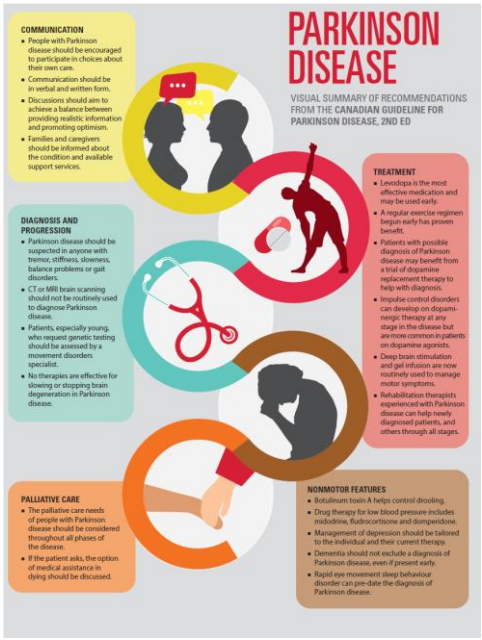
Results

Initial treatment with levodopa provides superior motor benefit compared to treatment with dopamine agonists, whereas levodopa is more likely than dopamine agonists to cause dyskinesia. The comparison of different formulations of dopamine agonists yielded little evidence that any one formulation or method of administration is superior. Long-acting forms of levodopa and levodopa with entacapone do not appear to differ in efficacy from immediate-release levodopa for motor symptoms in early disease. There is a higher risk of impulse control disorders associated with the use of dopamine agonists than levodopa. Recommendations on initial therapy for motor symptoms are provided to assist the clinician and patient in choosing between treatment options and to guide counseling, prescribing, and monitoring of efficacy and safety.

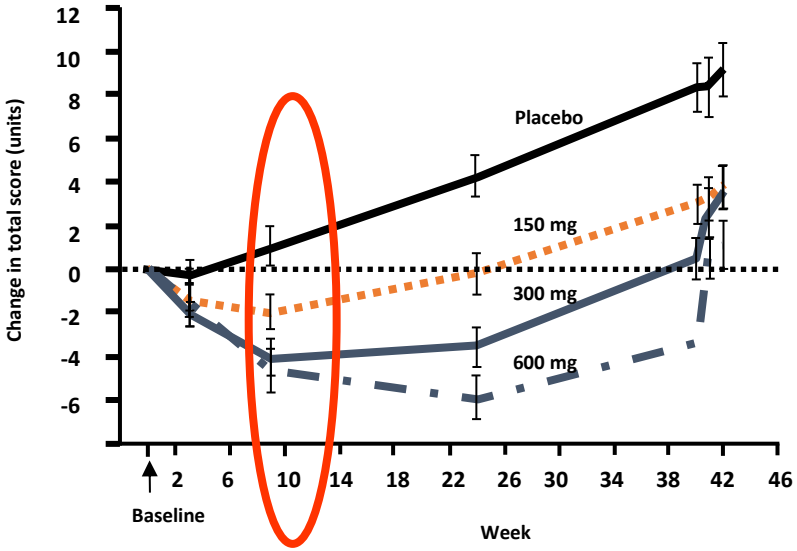
Canadian guideline for Parkinson disease

David Grimes MD, Megan Fitzpatrick MSc, Joyce Gordon BSc, Janis Miyasaki MD, Edward A. Fon MD, Michael Schlossmacher MD, Oksana Suchowersky MD, Alexander Rajput MD, Anne Louise Lafontaine MD, Tiago Mestre MD, Silke Appel-Cresswell MD, Suneil K. Kalia PhD, Kerrie Schoffer MD, Mateusz Zurowski MD, Ronald B. Postuma MD MSc, Sean Udow MD, Susan Fox PhD, Pauline Barbeau MSc, Brian Hutton PhD

Cite as: *CMAJ* 2019 September 9;191:E989-1004. doi: 10.1503/cmaj.181504



Low dose levodopa takes several weeks to work in early PD



Fahn S, *et al. N Engl J Med* 2004.

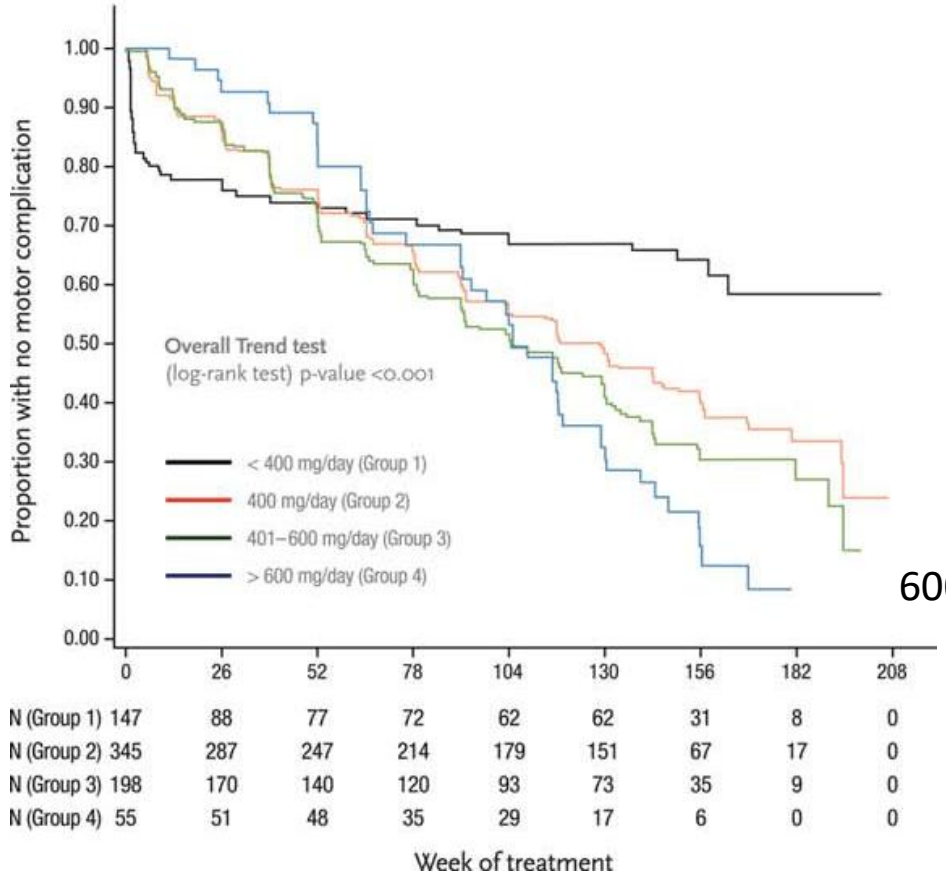

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levodopa and the Progression of Parkinson's Disease

The Parkinson Study Group*

Keep doses of Levodopa *low* to reduce risk of motor complications



300mg/day

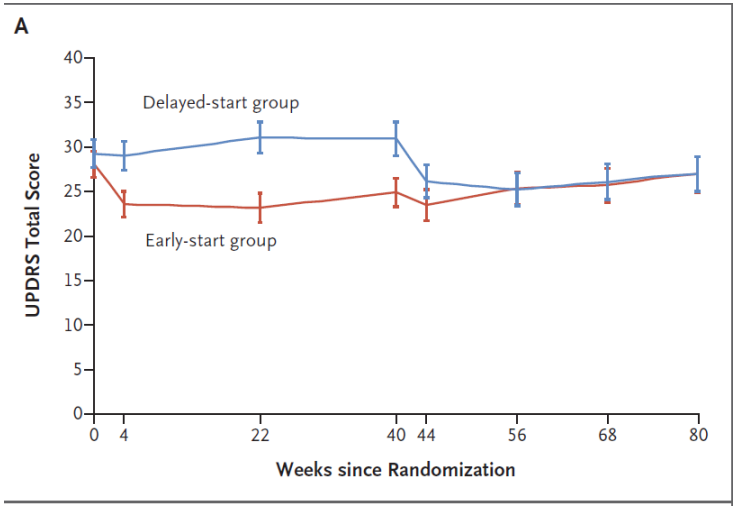
600mg/day

Factors Predictive of the Development of Levodopa-Induced Dyskinesia and Wearing-Off in Parkinson's Disease

Movement Disorders, Vol. 28, No. 8, 2013

Don't delay Levodopa if needed for symptom control

- **No disease modifying effects of levodopa**



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

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

C.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*

N Engl J Med 2019;380:315-24.

- **No difference** between groups in fluctuations or dyskinesia after 5y

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

RESEARCH ARTICLE | Open Access

Long-Term Follow-Up of the LEAP Study: Early Versus Delayed Levodopa in Early Parkinson's Disease

Henrieke L. Frequin MD, Constant V.M. Verschuur MD, Sven R. Suwijn MD, PhD, Judith A. Boel PhD, Bart Post MD, PhD, Bastiaan R. Bloem MD, PhD, Johannes J. van Hilten MD, PhD ... See all authors

First published: 21 April 2024 | https://doi.org/10.1002/mds.29796

TABLE 3 *Outcomes at 3- and 5-year follow-up*

Outcomes	Unadjusted Change from Baseline		Estimated Difference (SE)	*P* Value
	Early-Start Group	Delayed-Start Group		
3-Year follow-up				

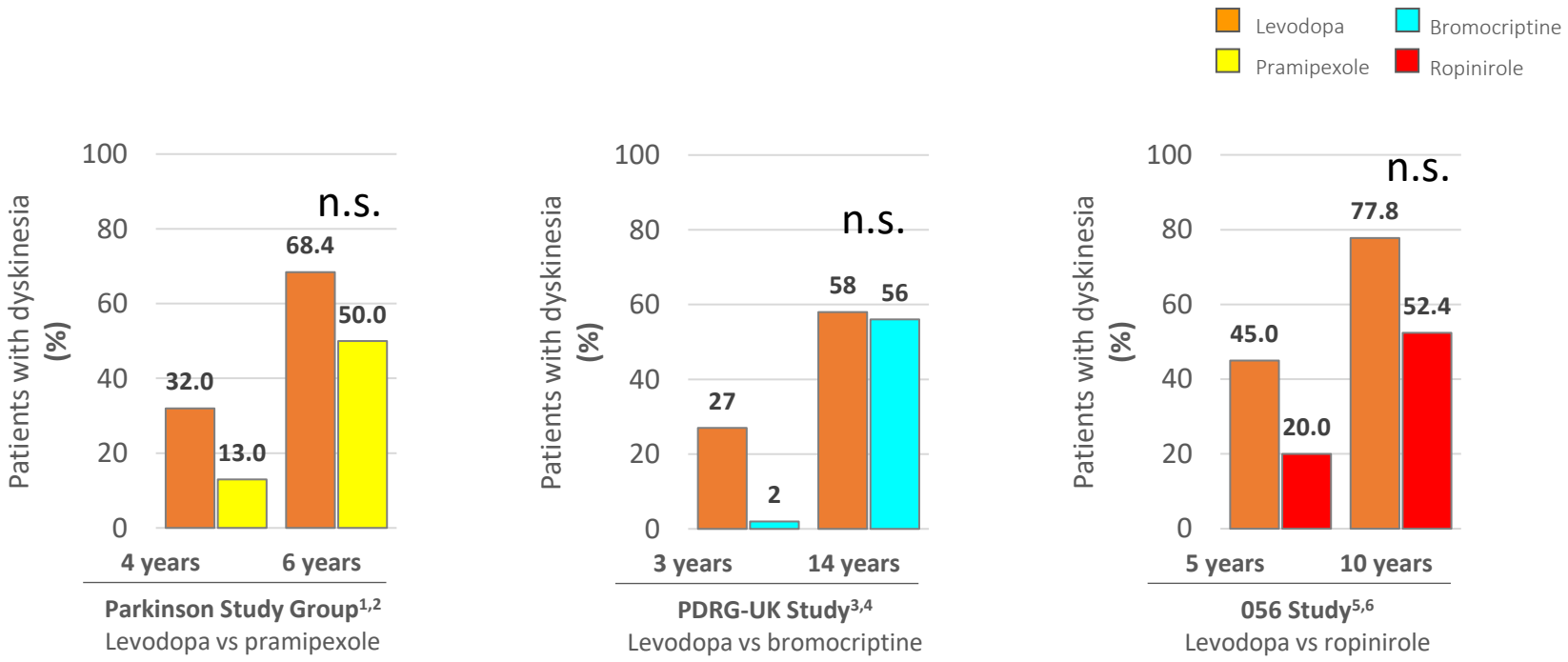
Dopamine Agonists

- Ropinirole p.o
- Pramipexole p.o.
- Rotigotine patch

- Apomorphine s.c.

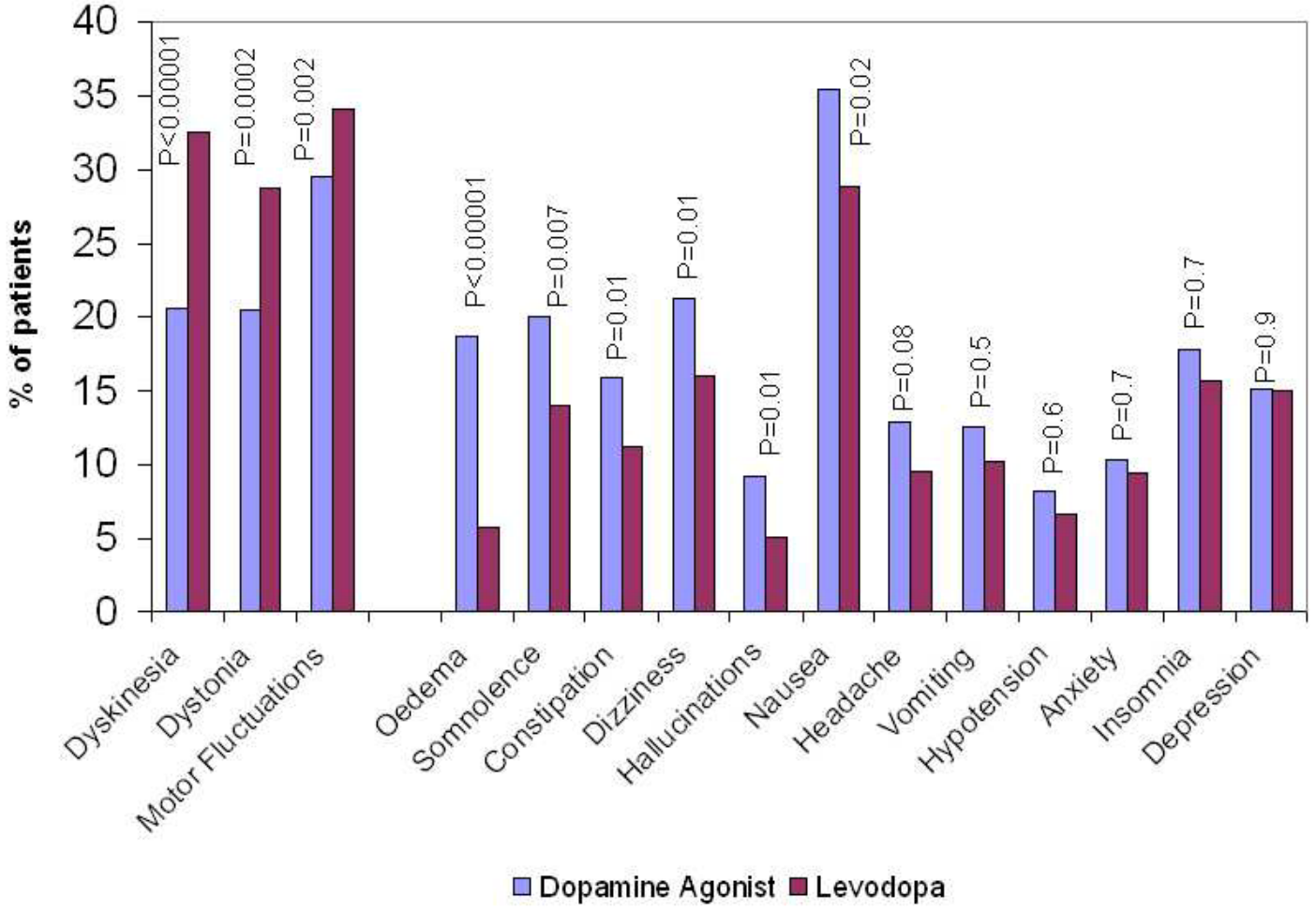
- Rationale for use:-
  - No interference from food absorption
  - Less risk of dyskinesia and motor fluctuations

Reduced risk of dyskinesia with initial DA vs levodopa is only in early years



Adapted from:1. PSG. Arch Neurol 2004;61:1044-53; 2. PSG. Arch Neurol 2009;66:563–70; 3. Parkinson's Disease Research Group UK. BMJ 1993;307:469–72; 4. Katzenschlager R et al. Neurology 2008;71:474–80; 5. Rascol O et al. N Engl J Med 2000;342:1484–91; 6. Hauser RA et al. Mov Disord 2007;22:2409–17

DA have more side effects



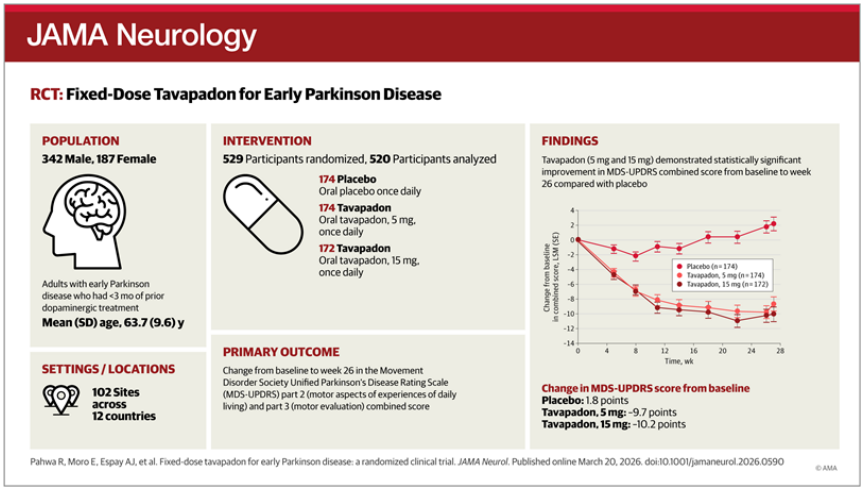
Cochrane Database of Systematic Reviews, Issue 1, 2009

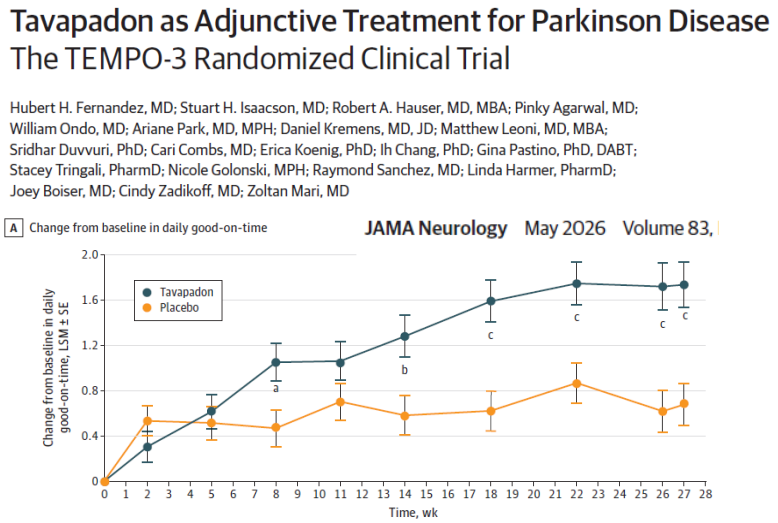
Always ask about Impulse Control Behaviours (ICB)

- ICBs include gambling, compulsive shopping, hypersexuality, and compulsive eating; hobbyism and punding
- Overall prevalence 5-40% (depending on methods and Geographic region)
- At risk = 5 ‘A’s
  - **A**ge: higher in younger
  - **A**ndrogens: male;
  - **A**ddiction - prior history (or +FH) of addiction.
  - **A**nxiety
  - **A**gonist> Levodopa (Punding = Levodopa higher risk)

- Possibly lower risk with rotigotine/pramipexole ER than shorter acting DA ? Rizos et al EJN 2016 https://doi.org/10.1111/ene.13034

Tavapadon: dopamine D1/D5 selective agonist





Early PD - monotherapy

Adverse events

Nausea 25%; headache 16%; dizziness 12%, OH 6%,

Hallucinations 3%

ICDs

0.8% v 0

1 withdrew

Adjunct

Adverse events

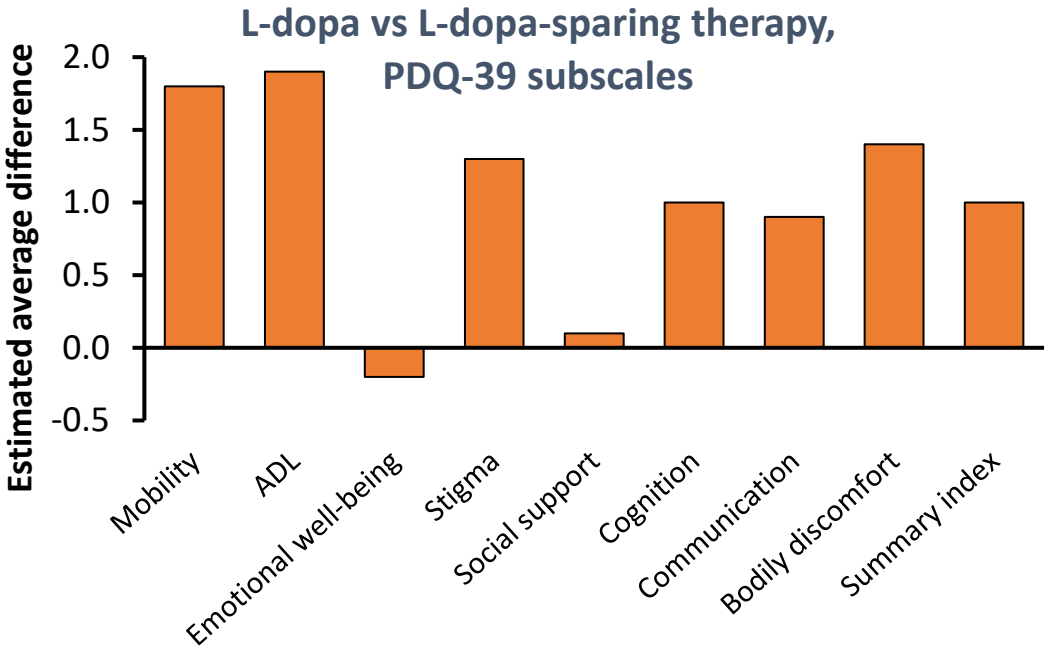
Nausea (14.3%), dyskinesia (10.0%), dizziness (7.6%), headache (6.8%), falls (6.4%), orthostatic hypotension (6.0%)

ICDs 2.4% (v 1.2% placebo).

1 withdrew

Levodopa is superior; "Real-World"' Clinical Trial Evidence

- 1620 early PD patients (UK)
- Randomised to:-
  - **Levodopa** (n= 528) Or
  - 'Levodopa Sparing' drug =
    - **Monoamine oxidase B inhibitor (MAOBI)** (selegiline or rasagiline)(n = 460) or
    - **Dopamine agonist (DA)** (n = 632)
  - 7y follow-up (median 3y)
  - Primary End point = **Parkinson's Disease Questionnaire PDQ39 (quality of life scale)**
    - **(Patient reported outcome)**



Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial

PD MED Collaborative Group*

www.thelancet.com Published online June 11, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60683-8

Motor Complications

- Predictable wearing-off
- Unpredictable off; sudden offs
- Dose failure, delayed or partial on response

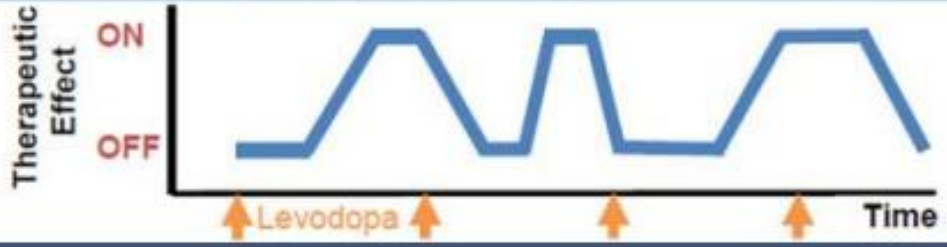
- Off-period and On-period freezing

- Beginning of dose worsening/'super-off'
-

- Dyskinesia
  - Peak dose/square wave dyskinesia
  - Wearing-off/ Off-period dystonia
  - Diphasic dyskinesia



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	

Mov Disordr 2018

Epidemiology of Motor Fluctuations

- **Off periods** affected 35.0% at 4–6 years; 59.0% at 8–10 years.
- **Dyskinesia** affected 18.5% at 4–6 years; 42.1% at 8–10 years.
- **Dystonia** affected 13.4% at 4–6 years; 22.8% at 8–10 years.

Motor complications were more common :-

  - higher drug doses,
  - younger age at diagnosis,
  - female gender,
  - greater dopaminergic responsiveness (in challenge tests)
- N = 3343 cases (64.7% male) for up to 13y (UK).

- Gandi et al 2024 https://doi.org/10.1002/mdc3.14044
- Sanros-Garcia et al Mov Disord 2024

Pathophysiology of levodopa-induced fluctuations

1. **Presynaptic loss of dopamine terminals** due to disease progression and neuroplasticity changes
2. **Peripheral pharmacokinetics leads to short half-life of levodopa due to**:
    - **Gastrointestinal (GI) factors**: dietary competition with protein in GI tract and across **blood–brain barrier**;
    - Slowed gastric emptying due to disease; constipation; anticholinergics; ?*Helicobacter pylori* infection
3. **Post-synaptic mechanisms** affecting dopamine and non-dopaminergic neurotransmission
    - **Abnormal pulsatile stimulation of post-synaptic dopamine receptors** leads to altered pattern of activity in medium spiny neurons in the striatum and maladaptive neuroplasticity

Expert Opinions on Treatments for PD

Parkinson's Disease 3

Medical, surgical, and physical treatments for Parkinson's disease

Tom Foltynie, Veronica Bruno, Susan Fox, Andrea A Kühn, Fiona Lindop, Andrew J Lees

Lancet 2024

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

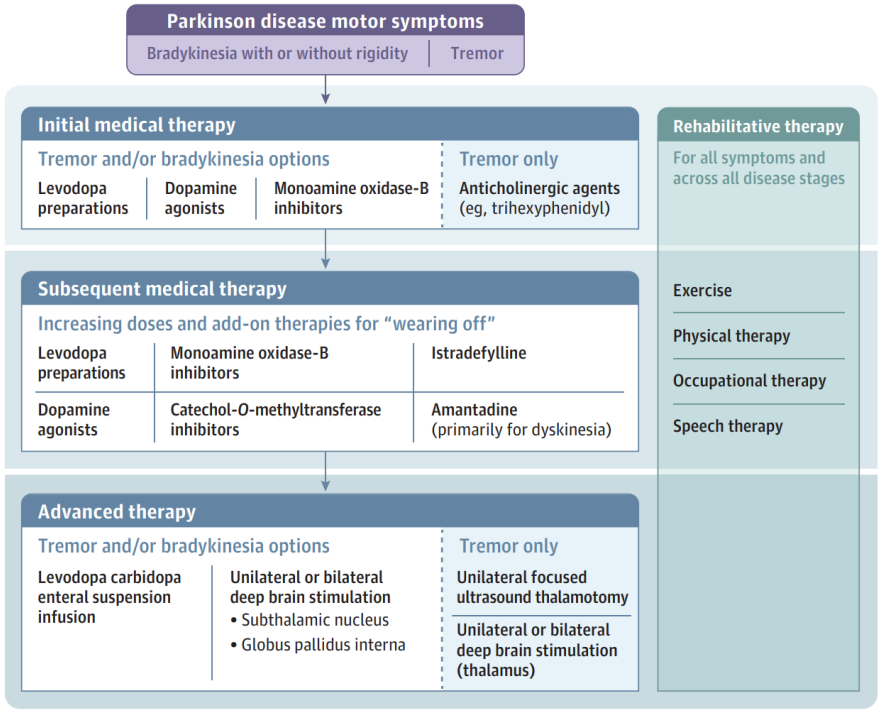
Allan H. Ropper, M.D., *Editor*

Parkinson's Disease

Caroline M. Tanner, M.D., Ph.D., and Jill L. Ostrem, M.D.

NEJM Aug 2024

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



JAMA | Review

Diagnosis and Treatment of Parkinson Disease
A Review

Melissa J. Armstrong, MD, MSc; Michael S. Okun, MD

JAMA February 11, 2020 Volume 323, Number 6

MDS-EBM Motor fluctuations

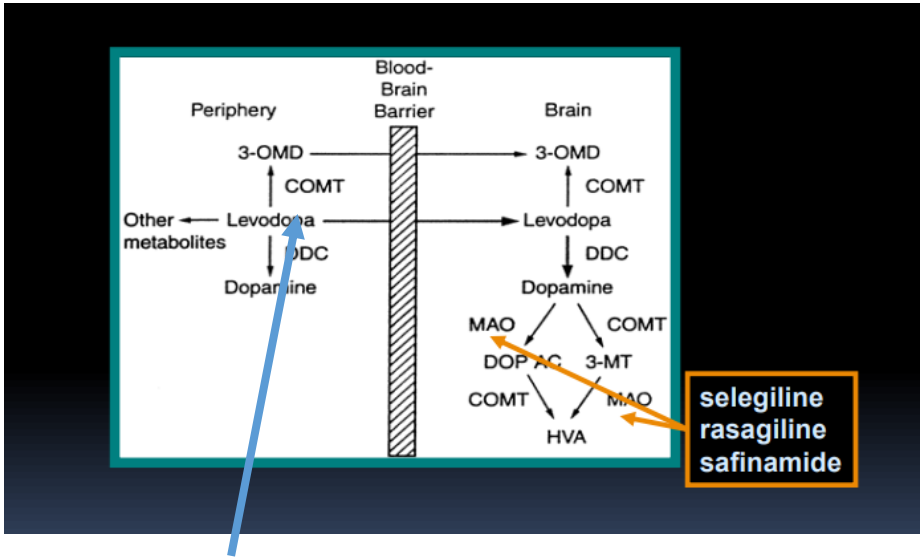
TABLE 2 *Efficacy conclusions of interventions for the treatment of motor fluctuations*

Class	Intervention	Efficacy conclusion	Safety[a]
Levodopa/PDI	Controlled release	Insufficient evidence	
	IPX066, ER	Efficacious	
	Intestinal infusion	Likely efficacious	Acceptable risk with specialized monitoring
	Subcutaneous infusion	Likely efficacious	
Dopamine agonists	Pramipexole IR	Efficacious	
	Pramipexole ER	Efficacious	
	Ropinirole IR	Efficacious	
	Ropinirole PR	Likely efficacious	
	Ropinirole patch	Likely efficacious	
	Rotigotine	Efficacious	
	Apomorphine continuous	Likely efficacious	Acceptable risk with specialized monitoring
	Apomorphine intermittent	Insufficient evidence	
COMT inhibitors	Entacapone	Likely efficacious	
	Opicapone	Efficacious	
MAO-B inhibitors	Rasagiline	Likely efficacious	
	Selegiline	Insufficient evidence	
MAO-B inhibitor plus channel blockers	Safinamide	Efficacious	

De Bie et al Mov Disord 2025

Others	Istradefylline	Likely efficacious	
	Amantadine IR	Insufficient evidence	
	Amantadine CR	Likely efficacious	
	Terguride	Insufficient evidence	
	Nicotine	Insufficient evidence	
	Zonisamide	Likely efficacious	
	Perampanel	Insufficient evidence	
	Helicobacter pylori eradication	Insufficient evidence	
	Coenzyme Q10	Not efficacious	
	Exenatide	Insufficient evidence	
Surgery	Bilateral STN DBS	Efficacious	Acceptable risk with specialized monitoring
	Bilateral GPi DBS	Likely efficacious	
	Unilateral pallidotomy	Likely efficacious	
	Subthalamotomy	Insufficient evidence	
	Bilateral zona incerta DBS	Insufficient evidence	
	GDNF	Insufficient evidence	

Addition of MAOB-I, COMT-I or DA will improve motor fluctuations…



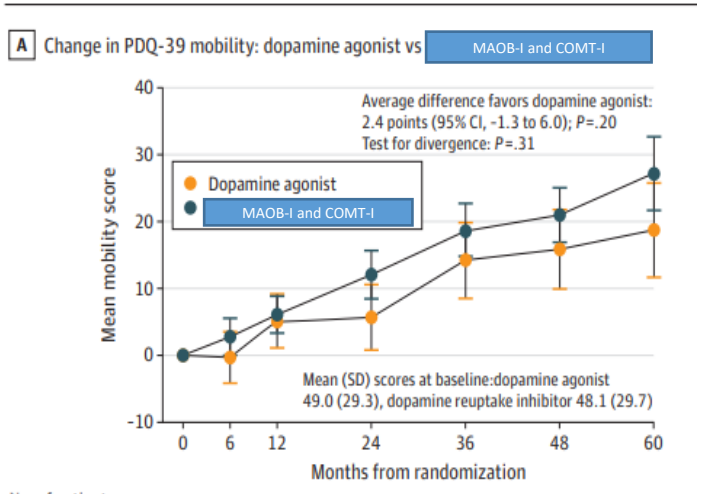
Entacapone
Opicapone

Factors influencing choice?

1. Benefit on fluctuations
2. Ease of use
3. Side-effects
4. Cost/Availability

“Real-World” Evidence

- 500 patients with PD uncontrolled motor complications on Levodopa
- Randomised to: -
  - **Dopamine agonist (DA), MAO-B inhibitor (MAOBI), or COMT inhibitor (COMT-I) as Add –On to levodopa.**
- Follow-up
  - median 4.5 years (range, 0-13.3 years)



- Primary outcomes
  - 39-item Parkinson’s Disease Questionnaire (PDQ-39)

- **COMT- I inferior compared with MAO-B inhibitors or dopamine agonists**
- **DA – better mobility scores (n.s.)**
- **MAOB-I similar outcome to DA**


JAMA Neurology | Original Investigation

Long-term Effectiveness of Adjuvant Treatment With Catechol-O-Methyltransferase or Monoamine Oxidase B Inhibitors Compared With Dopamine Agonists Among Patients With Parkinson Disease Uncontrolled by Levodopa Therapy
The PD MED Randomized Clinical Trial

Richard Gray, MSc; Smitaa Patel, MSc; Natalie Ives, MSc; Caroline Rick, PhD; Rebecca Woolley, MSc; Sharon Muzerengi, MD; Alastair Gray, DPhil; Crispin Jenkinson, DPhil; Emma McIntosh, PhD; Keith Wheatley, DPhil; Adrian Williams, MD; C. E. Clarke, MD; for the PD MED Collaborative Group

JAMA Neurol. 2022;79(2):131-140. doi:10.1001/jamaneurol.2021.4736

……Side effects?

- **Dopamine Agonists**
  - Sleep, Low BP, Hallucinations, ICB …..
- **COMT-I**
  - Urine discolouration; GI upset (diarrhoea);
  - risk of dyskinesia (15%)
- **MAOB-I**
  - risk of dyskinesia (15%).
  - Theoretical risk of Serotonin syndrome (very very rare)

On Serotonin Syndrome, Antidepressants and MAOB-Is?

Allowed in Clinical Trials of Rasagiline

Drug	Dose of antidepressant allowed in Clinical trial of Rasagiline
Sertraline	≤100 mg
Paroxetine	≤30 mg
Citalopram	≤20 mg
Escitalopram	≤10 mg
Fluvoxamine	≤150 mg
Trazodone	≤100 mg
Amitriptyline	≤50 mg

Rasagiline clinical trials did not allow concomitant use of fluoxetine or venlafaxine

Literature review SSRIs and MAOBI

Risk of serotonin syndrome is very low
"Serotonin syndrome occurs rarely……

Selegiline and Fluoxetine are combinations where cases are reported …Therefore, SSRIs and MAO-B inhibitors can be co-administered, provided SSRI dose is kept at the lower end of the therapeutic range".

Aboukarr and Guidice Can J Hosp Pharm 2019

Hattori et al Curr Opin Drug Saf 2024

Phase IV safety with rasagiline

EXPERT OPINION ON DRUG SAFETY
2024, VOL. 23, NO. 1, 79–88
https://doi.org/10.1080/14740338.2023.2293207

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Safety and effectiveness of rasagiline in patients with Parkinson's disease in Japan: a post-marketing surveillance study

Nobutaka Hattori[a], Mika Kajita[b], Shinji Fujimoto[b], Miwa Izutsu[b] and Jovelle Fernandez[b†]

[a]Department of Neurology, Juntendo University Graduate School of Medicine, Tokyo, Japan; [b]Japan Medical Office, Takeda Pharmaceutical Company Limited, Tokyo, Japan

- N = 950 Japan PD
- ≥80 years plus dementia were included.
- Mono **<< Adjunct therapy**; 865 (90.01%) patients on levodopa
- Commonest Adverse Drug Reactions =
  - dyskinesia (4.06%, 39/961 patients),
  - orthostatic hypotension (2.29%, 22/961 patients),
- **No Serotonin Syndrome**

Drug Safety (2023) 46:637–646
https://doi.org/10.1007/s40264-023-01288-2

ORIGINAL RESEARCH ARTICLE

Check for updates

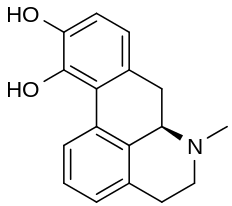
Safety and Effectiveness of Rasagiline in Chinese Patients with Parkinson's Disease: A Prospective, Multicenter, Non-interventional Post-marketing Study

Wen Su[1,2,3] · Zhanhua Liang[4] · Wei Mao[5] · Ming Shao[6] · Xingyue Hu[7] · Yuncheng Wu[8] · Wenshi Wei[9] · Zhenguo Liu[10] · Kezhong Zhang[11] · Beisha Tang[12] · Shuai Cao[13] · Zhuolun Song[13] · Haibo Chen[1,2,3]

- N = 745 China PD
- Age 64.0 ± 10.15 y
- **Mono** >> Adjunct therapy 26.8% on anti-PD
- ADRs were comparable between the monotherapy (15.8%) and adjunct therapy (13.6%) subgroups.
- Commonest ADRs
  - nervous system disorders (5.6%),
  - gastrointestinal disorders (3.3%),
  - psychiatric disorders (1.8%),
- **No Serotonin syndrome**

EXPERT OPINION ON DRUG SAFETY2024, VOL. 23, NO. 1, 79–88; Drug Safety (2023) 46:637–646

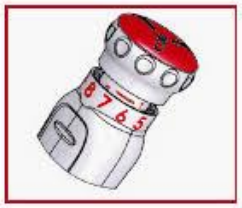
Apomorphine: Old Drug; New Tricks?



- **Erectile dysfunction** - first described by Ancient Egyptians (naturally occurring in blue lotus *N. caerulea*)
- **Emetic –** Alcoholism - 'The Keeley Cure' (1870s to 1900) contained Apomorphine.
- **Parkinson's disease**
  - First described by Weil, 1884
  - Schwab RS, Amador LV, Lettvin JY (1951). Apomorphine in Parkinson's disease. Transactions of the American Neurological Association. **56**: 251–3
- Subcutaneous Intermittent (and pump) for OFF treatment as adjunct
- Licensed in many countries;:
- Europe/UK since 1980s;
- US 2004 – intermittent ; Pump 2025
- Canada 2019 (no longer marketed)

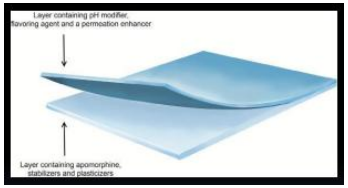
- Non-ergot dopamine agonist
- Low oral bioavailability (first pass metabolism)
- Prior failures with
  - Intravenous; Nasal; rectal
    - Local skin reactions
      - Acidic; pH 3.0 to 4.0
      - Intravenous - crystallizes causing thrombosis





Treatments for Acute OFFs







CRITERIA	Subcutaneous Apomorphine	Sublingual Apomorphine	Inhaled Levodopa
RAPID	**+++ Onset 10 -15 min**	+ Onset <30min	++ Onset (10-30min)
BEST MOTOR RESPONSE	**+++ 20 MIN (–22)#**	++ 30 MIN (- 8)#	+ 30 MIN (- 3.4)#
RELIABLE	**+++ (OFF to ON in 95%)**	++ (OFF to ON 79%)	++ (‘Most” ON at 60 min 58%)
SIDE EFFECTS	++	++	**+**
ROUTE of administration and Ease of Use	+ INJECTION	**+++ SUBLINGUAL STRIP**	++ INHALER
	Premed with anti-nausea In clinic titration	Premed with anti-nausea in clinic titration	No titration. 84mg max dose

\+ least
++ Moderate/intermediate
+++ Best

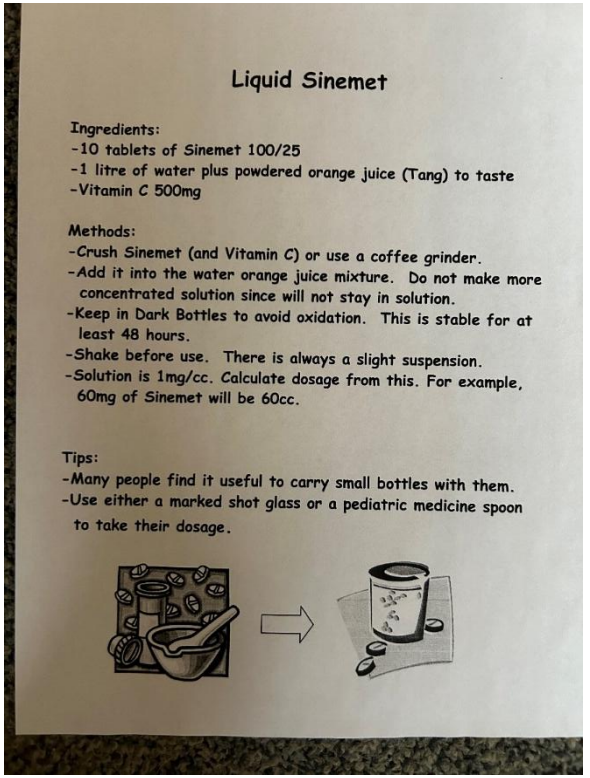
#mean change in UPDRS vs placebo

Adapted from:
On Demand Therapy for OFF episodes in Parkinson Disease Olanow et al Mov Disord Oct 2021

Crushed Levodopa/carbidopa IR

- Crushed with apple sauce and carbonated water





Liquid Sinemet

Ingredients:
-10 tablets of Sinemet 100/25
-1 litre of water plus powdered orange juice (Tang) to taste
-Vitamin C 500mg

Methods:
-Crush Sinemet (and Vitamin C) or use a coffee grinder.
-Add it into the water orange juice mixture. Do not make more concentrated solution since will not stay in solution.
-Keep in Dark Bottles to avoid oxidation. This is stable for at least 48 hours.
-Shake before use. There is always a slight suspension.
-Solution is 1mg/cc. Calculate dosage from this. For example, 60mg of Sinemet will be 60cc.

Tips:
-Many people find it useful to carry small bottles with them.
-Use either a marked shot glass or a pediatric medicine spoon to take their dosage.

Mucuna Puriens - ? helpful

- RCT high-dose (17.5 mg/kg);
  - acute benefit v levodopa
  - Cilia et al 2017
- Longer term 16 w;
  - 50% drop-outs - GI side effects or lack of benefit
  - Cilia et al 2018
- Caution - variable content in OTC products

JAMA Neurol. 2022;79(10):1085-1086. doi:10.1001/jamaneurol.2022.2184

Table. Information Regarding *Mucuna pruriens* Seed Extract on Labels of Dietary Supplements Compared With Quantity Detected in Analyzed Samples of Supplements

Claim on label	Description of *M pruriens* according to label	Amount per serving size of *M pruriens* seed extract according to label, mg	Measured levodopa per serving size, mean (SD), mg/estimated levodopa per serving size, mg [%][a]
Strength, power, performance	*M pruriens* seed extract; std to 98% naturally occurring levodopa	150	129.1 (0.2)/5.9 [2186]
Brain support	*Mucuna* seed extract (*M pruriens*); std to contain 60% levodopa (3,4 dihydroxy-L-phenylalanine)	425	241 (0.3)/16.6 [1452]
Preworkout	*M pruriens*; std 98% levodopa	NA	78.9 (0.5)/NP
Brain support	*Mucuna* extract (*Mucuna* spp seed); minimum 15% naturally occurring levodopa or levodopa	800	154.2 (0.3)/31.2 [494]
No claim	Organic *M pruriens* seed extract 10:1; 15% naturally occurring levodopa	250	53.1 (0.3)/9.8 [544]
Positive mood, mental clarity and focus, performance, hormone health	Natural *M pruriens* seed extract	1000	94.4 (1.0)/39 [242]
Supports dopamine production and motivation	*M pruriens* seed extract	250	93.8 (0)/9.8 [957]
Fat metabolism, appetite control, focus and stimulation	*M pruriens* seed extract	NA	31.5 (1.1)/NP
Dopamine and serotonin boosters	Mucuna (*M pruriens*) bean	NA	56.2 (0.1)/NP
Cognitive support	*M pruriens* seed extract	600	53.4 (0.8)/23.4 [228]
Dopamine bean	Mucuna (*M pruriens*) bean	NA	17.3 (0.5)/NP
Natural source of energy	*M pruriens* seed extract; std to contain minimum 50% levodopa	95	12.4 (0.5)/3.7 [335]
Rest and rejuvenation support	*M pruriens*; 15% extract (seed)	50	7.4 (1.2)/2.0 [370]
Fat burner	*M pruriens*; std to 98% levodopa	NA	2.0 (0.2)/NP
Deep calm	*M pruriens* (seed)	NA	3.4 (0.3)/NP
Adaptogen	Organic Mucuna (*M pruriens*) seed extract 20:1	NA	Not detected/NP[b]

Abbreviations: NA, not available; NP, not possible (estimate not possible given lack of declared quantity of *M pruriens* seed extract on label); spp, species; std, standardized.

[a] Estimated quantity of levodopa calculated by multiplying the declared quantity of the *M pruriens* seed extract listed on the label (in mg) by the highest percentage of levodopa found in the extracts of authenticated *M pruriens* seeds (3.9%).

[b] Detection limit of 50 ng/mL for levodopa.

Longer-acting levodopa formulations

- **Oral**
  - IPX203
- **Infusions**
  - Levodopa/carbidopa i.j. gel
  - Foslevodopa/foscarbidopa s.c
  - *ND0612: levodopa/carbidopa s.c*
    - *Giladi et al PRD 2021*

Longer acting oral Levodopa IPX203

- IPX203 (140 mg LD:35 mg CD) 3/d vs IR CD-LD vs placebo/placebo 5/d . DBRCT, double-dummy
- Initial 3-4w titration then 13 w DBRCT
- PD 506 with 2.5h OFF time
- Improved Good on-time v IR (**0.53 hours**)
- AE =Nausea/anxiety/dizziness
- Approved Aug 2024 - US

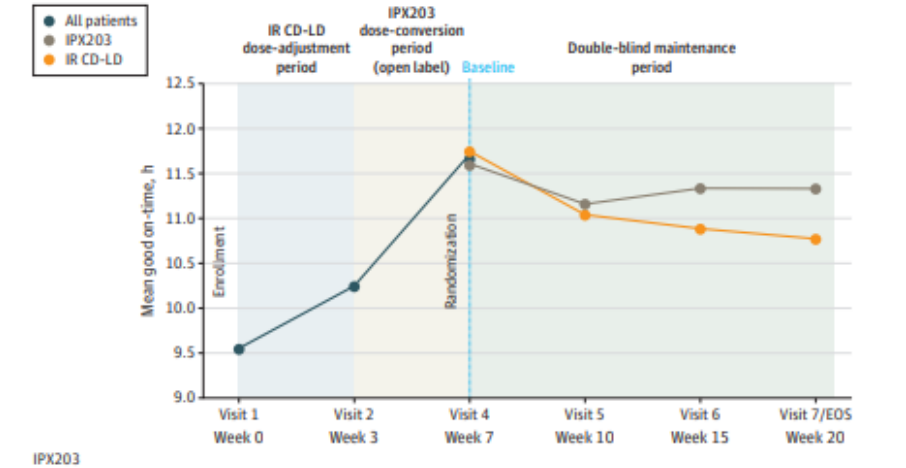
JAMA Neurology | Original Investigation

IPX203 vs Immediate-Release Carbidopa-Levodopa for the Treatment of Motor Fluctuations in Parkinson Disease
The RISE-PD Randomized Clinical Trial

Robert A. Hauser, MD, MBA; Alberto J. Espay, MD; Aaron L. Ellenbogen, DO; Hubert H. Fernandez, MD; Stuart H. Isaacson, MD; Peter A. LeWitt, MD; William G. Ondo, MD; Rajesh Pahwa, MD; Johannes Schwarz, MD; Fabrizio Stocchi, MD; Leonid Zeitlin, PhD; Ghazal Banisadr, PhD; Stanley Fisher, MD; Hester Visser, MD, PhD; Richard D'Souza, PhD

JAMA Neurol. doi:10.1001/jamaneurol.2023.2679
Published online August 14, 2023.

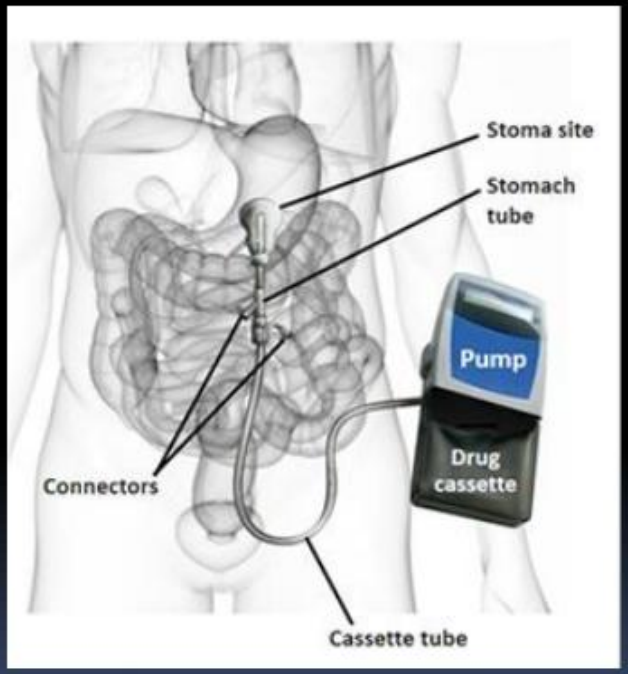
Figure 3. Change From Baseline in Good On-Time, Least Squares Mean



	Visit 1 Week 0	Visit 2 Week 3	Visit 4 Week 7	Visit 5 Week 10	Visit 6 Week 15	Visit 7/EOS Week 20
IPX203						
Total, No.	249	248	249	237	222	235
Median (range), h	9.5 (1.7-14.8)	10.33 (1.5-16.5)	12.0 (0.5-18.8)	11.5 (0-18.3)	11.67 (0-19.3)	11.5 (0-17.7)
IR CD-LD						
Total, No.	246	245	246	235	227	241
Median (range), h	9.67 (0.5-15.8)	10.33 (0.2-15.8)	11.67 (1.8-18.0)	11.17 (0-18.3)	10.67 (0-18.3)	10.83 (1.5-17.0)

Levodopa gel intrajejunal infusions Duopa ®

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



Slide courtesy Dr C. Comella

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

Taher et al Can J Neurol Sci 2022

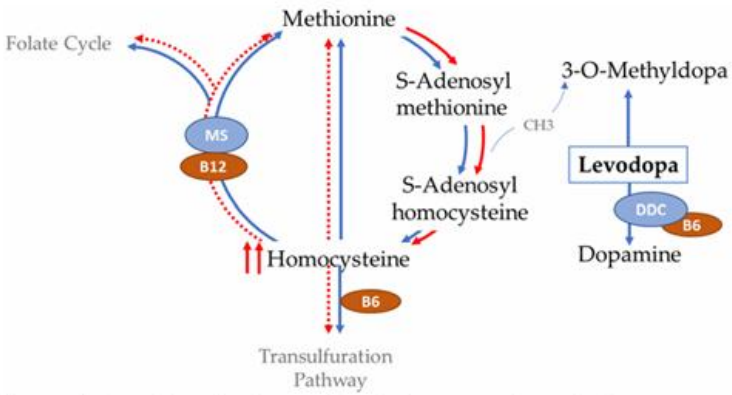


Figure 4. *Levodopa depletion of methyl reserves from the homocysteine metabolic pathway. DDC, dopamine decarboxylase; MS, methionine synthase. Adapted from Refs.5,59*

Table 3: Synopsis of laboratory results in vitamin B6, B9 (folate), and B12 deficiency*

Deficiency	First-line screening			Second-line screening	
	Vitamin B12	**Homocysteine**	**MMA**	**Vitamin B6**	**Folate**
Vitamin B6	↔	↑	↔	↓	↔
Folate	↔	↑	↔	↔	↓
Vitamin B12	↓	↑	↑	↔	↔/↓
Note	Needs to be dosed before testing folate (*Methyltrap*)	May be elevated in advanced age, renal insufficiency, hypovolemia, hypothyroidism, psoriasis, and inherited metabolic disorders	May be elevated in renal insufficiency, hypovolemia, patients over 65 yrs and inherited metabolic defects	Not always available, expensive	Not always available, expensive. False negatives occurring in vitamin B12 deficiency (*Methyltrap*)

Abbreviations: *Cell blood count is not useful as neurological symptoms sometimes presenting in the absence of hematological changes; MMA, methylmalonic acid.

Treatment

- Oral doses of the deficient vitamin at bedtime**
  - Cyanocobalamin: 1000 mg/day
  - Folic acid: 5–15 mg/day***
  - Pyridoxine: 50–100 mg/day*

Taher et al CJNS 2022

Subcutaneous Fos-Levodopa/Carbidopa

Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial

Michael J Soileau, Jason Aldred, Kumar Budur, Nahome Fisseha, Victor SC Fung, Anna Jeong, Thomas E Kimber, Kevin Klos, Irene Litvan, Daniel O'Neill, Weining Z Robieson, Meredith A Spindler, David G Standaert, Saritha Talapala, Eleni Okeanis Vaou, Hui Zheng, Maurizio F Facheris, Robert A Hauser

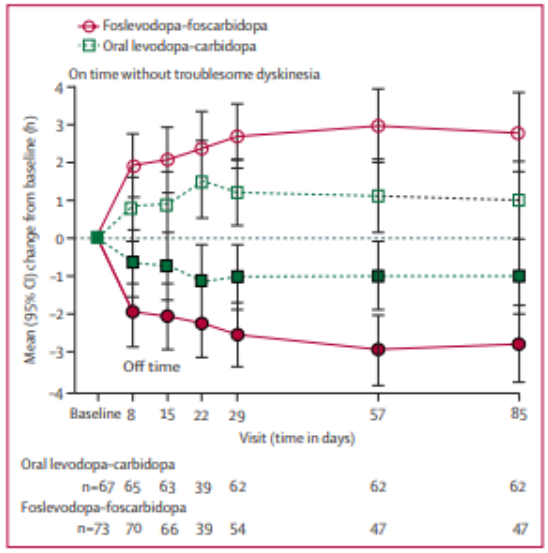


Figure 2: **Least squares mean (95% CI) of change from baseline in average daily on time without troublesome dyskinesia and off time (full analysis set)**

Lancet Neurol 2022; 21: 1099-109

ABBV 951 s.c + IR LD/CD p.o. v placebo s.c/p.o

12 w

145, PD with fluctuations

Increase On time without troublesome dyskinesia (+ **1·75 h)**

- Reduced off time (difference **–1·79 h**).
  - No significant change in MDS-UPDRS II
- Side effects: infusion site reactions erythema (27%), pain [26%], cellulitis [19%]; oedema [12%]).

- **Needle change every 1-3 days**
- **s/c Levodopa equivalent to oral levodopa**
- **Care! Skin reactions and hallucinations**

Subcutaneous Levodopa/carbidopa

Safety and efficacy of continuous subcutaneous levodopa–carbidopa infusion (ND0612) for Parkinson's disease with motor fluctuations (BouNDless): a phase 3, randomised, double-blind, double-dummy, multicentre trial

Alberto J Espay, Fabrizio Stocchi, Rajesh Pahwa, Alberto Albanese, Aaron Ellenbogen, Joaquim J Ferreira, Nir Giladi, Tanya Gurevich, Sharon Hassin-Baer, Jorge Hernandez-Vara, Stuart H Isaacson, Karl Kieburtz, Peter A LeWitt, Lydia Lopez-Manzanares, C Warren Olanow, Werner Poewe, Harini Sarva, Tami Yardeni, Liat Adar, Laurence Salin, Nelson Lopes, Nissim Sasson, Ryan Case, Olivier Rascol, * on behalf of the BouNDless Study Group†*

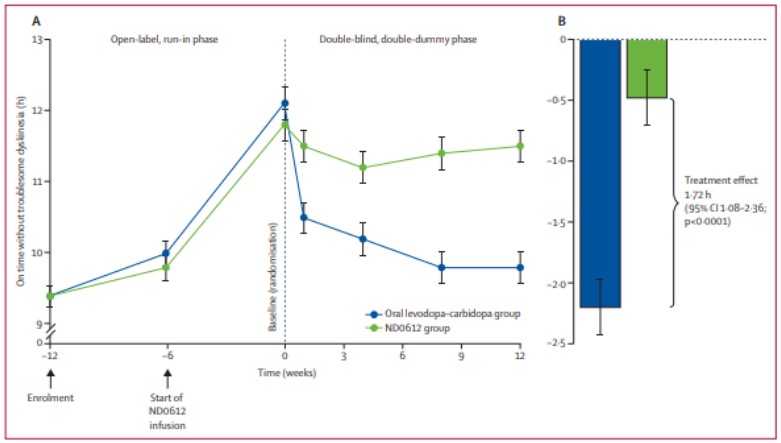


Figure 2: **Change in on time without troublesome dyskinesia during the study (primary efficacy endpoint)**
(A) Change in least-squares mean on time without troublesome dyskinesia from enrolment (−12 weeks) to study endpoint (12 weeks). Error bars are SE. On time was assessed with a 24 h self-completed home 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. (B) Treatment difference from randomisation visit (week 0) to study endpoint (week 12). Error bars are 95% CI.

- ND0612 SC infusion v IR-LD/CD. DBRCT double dummy
- 12 w
- 380; Fluctuations > 2.5h off time/d
- Increased ON time without troublesome dyskinesia **+ 1.72h**.
- Reduced OFF-time **-1.40h**
  - MDS-UPDRS Part II -3.05 p<0.0001)
- Infusion site reactions: 84.2% during open-label conversion to infusion, during the DBDD 57.0% for ND0612 vs. 43.5% for IR-LD/CD).

- **Maximal Levodopa 720mg**
- **(still) Pending FDA approval**

Stem cells for dopamine replacement ?

Phase I/II trial of iPS-cell-derived dopaminergic cells for Parkinson's disease

https://doi.org/10.1038/s41586-025-08700-0
Received: 9 August 2024
Accepted: 24 January 2025
Published online: 16 April 2025
Open access

Nobukatsu Sawamoto[1,8], Daisuke Doi[2,8], Etsuro Nakanishi[1,8], Masanori Sawamura[1,8], Takayuki Kikuchi[3], Hodaka Yamakado[1], Yosuke Taruno[1], Atsushi Shima[1], Yasutaka Fushimi[4], Tomohisa Okada[4], Tetsuhiro Kikuchi[2], Asuka Morizane[2], Satoe Hiramatsu[2], Takayuki Anazawa[5], Takero Shindo[6], Kentaro Ueno[7], Satoshi Morita[7], Yoshiki Arakawa[3], Yuji Nakamoto[4], Susumu Miyamoto[3], Ryosuke Takahashi[1]✉ & Jun Takahashi[2]✉

- N = 7
- Bilateral transplant of dopamine progenitors from IPS cells (healthy donor) into putamen
- Immunosuppression
- Safety and tolerability
- No SAEs (No tumour)
- MDS-UPDRS III improved by av 9 points (OFF)
- ^{18}F FlurodopaPET 44% increase in signal in putamen
- **Raguneprocel – limited approval in Japan**

Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease

https://doi.org/10.1038/s41586-025-08845-y
Received: 26 July 2024
Accepted: 26 February 2025

V. Tabar[1,2,3]✉, H. Sarva[4], A. M. Lozano[5,6], A. Fasano[6,7,8], S. K. Kalia[5,6], K. K. H. Yu[1], C. Brennan[1], Y. Ma[9,10], S. Peng[9], D. Eidelberg[9,10], M. Tomishima[11], S. Irion[11], W. Stemple[11], N. Abid[11], A. Lampron[11], L. Studer[2,12,14] & C. Henchcliffe[13,14]

- N = 12
- Bilateral transplant of human embryonic stem cells (bemdanmeprocel) into putamen
- Immunosuppression
- Safety and tolerability
- No SAEs (no GID)
- MDS-UPDRS III improved by av 8.6 points (OFF)
- ^{18}F FlurodopaPET increase in signal in putamen ? Amount
- **Ongoing Phase III RCT**

DYSKINESIA
DISCINESIA



'Disco.'

Unintended, involuntary, and uncontrollable movements. They are rapid and dance – like.

Movimientos no intencionales, involuntarios e incontrolables. Son rápidos y parecidos a la danza.

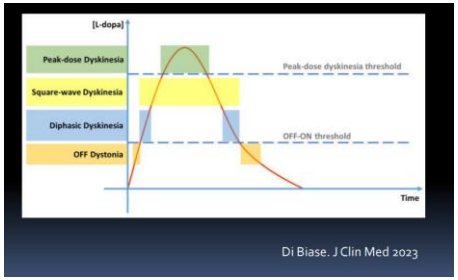
Levodopa-induced dyskinesia

‘High-dose’ dyskinesia

- Peak-dose dyskinesia
- ON period dyskinesia
- Phenomenology
  - Chorea – neck, limbs;trunk
  - Dystonia – limbs/neck
  - Myoclonus

‘Low-dose’ dyskinesia

- Diphasic dyskinesia (Beginning and end-of-dose dyskinesia)
- OFF period and wearing-off dystonia
- Phenomenology
  - Dystonia - foot
  - High amplitude ballistic movements



MDS-EBM Recommendations for Levodopa – induced Dyskinesia

TABLE 5b. Treatments for dyskinesia

Class	Intervention	Efficacy conclusions	Safety[a]	Implications for clinical practice
Dopamine agonists	**Pramipexole**	Insufficient evidence		Investigational
Levodopa/peripheral decarboxylase inhibitor	**Intestinal infusion**	Likely efficacious	Acceptable risk with specialized monitoring	*Clinically useful*
Others	**Amantadine**	Efficacious		Clinically useful
	Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Zonisamide	Insufficient evidence		Investigational
	Levetiracetam	***Insufficient evidence***		***Investigational***
Surgery	**Bilateral STN DBS**	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Bilateral GPi DBS	Efficacious		Clinically useful
	Unilateral pallidotomy	Efficacious		Clinically useful
	Unilateral thalamotomy	Insufficient evidence		Investigational
	Thalamic stimulation (uni or bilateral)	Insufficient evidence		Investigational
	Subthalamotomy	Insufficient evidence		Investigational
	Human fetal transplantation	Nonefficacious	Unacceptable risk	investigational
Nonpharmacological	**Physical therapy**	***Insufficient evidence***		***Investigational***

MDS-EBM Recommendations for Levodopa – induced Dyskinesia

TABLE 5b. Treatments for dyskinesia

Class	Intervention	Efficacy conclusions	Safety[a]	Implications for clinical practice
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	Unilateral thalamotomy	Insufficient evidence		Investigational
	Thalamic stimulation (uni or bilateral)	Insufficient evidence		Investigational
	Subthalamotomy	Insufficient evidence		Investigational
	Human fetal transplantation	Nonefficacious	Unacceptable risk	investigational
Nonpharmacological	Physical therapy	*Insufficient evidence*		*Investigational*

Amantadine

- Effects in Parkinson disease
  - Modest benefit for the motor symptoms of PD
  - Reduce dopamine induced dyskinesias in PD
    - Doses 200-400mg in divided doses
  - Caveat : secreted unchanged through kidney. Caution in renal insufficiency or failure
  - Side effects
    - Anticholinergic, leg swelling, livedo reticularis, hallucinations



Slide Courtesy of Dr Cindy Comella

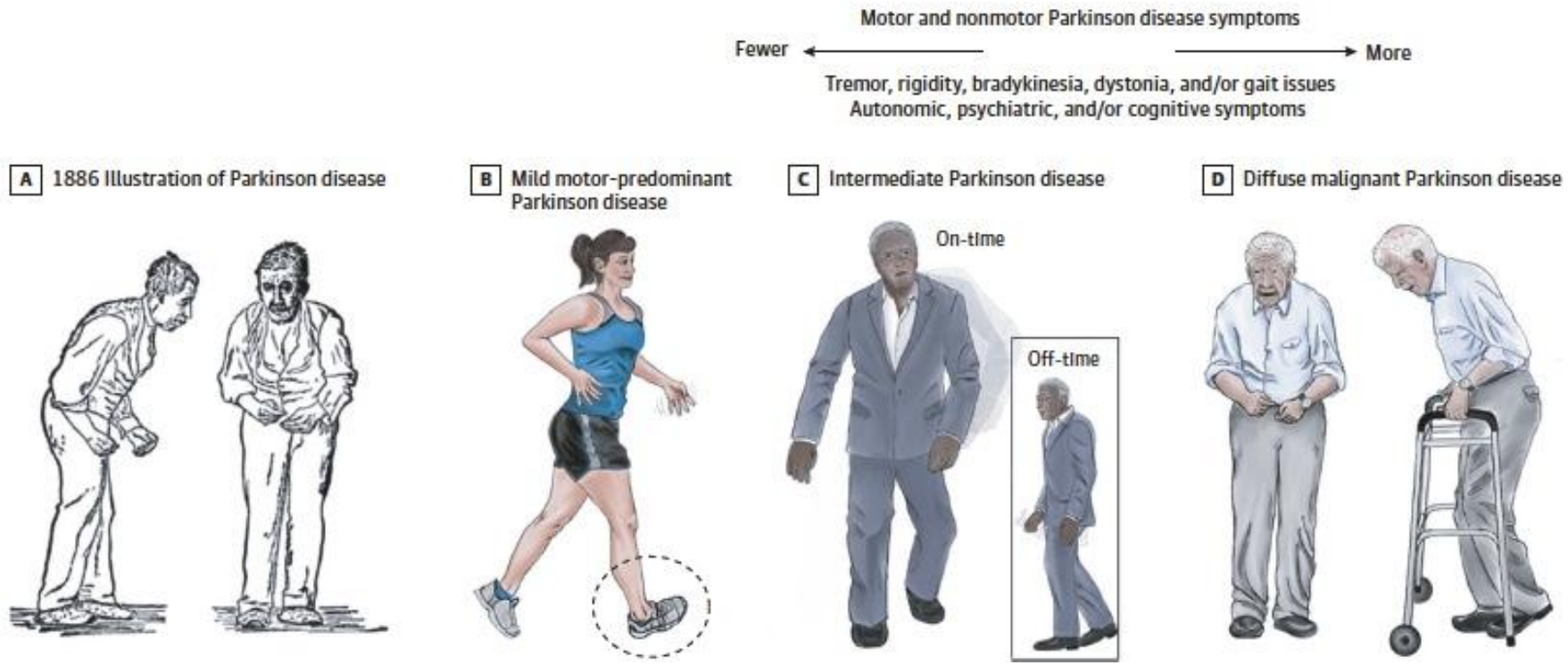
Yan et al Treatment for Dyskinesia in Parkinson's Disease: A Network Meta-analysis of Randomized Controlled Trials Mov Disord 2025

- Ranked according to effectiveness

1. Globus pallidus interna deep brain stimulation (GPi-DBS)
2. levodopa-carbidopa intestinal gel infusion
3. subthalamic nucleus (STN)-DBS
4. immediate-release (IR) amantadine
5. pallidotomy
6. Extended amantadine
7. clozapine

Parkinson Disease

Figure. Images of Parkinson Disease: 1886 and 2020



Armstrong M, Okun M, JAMA Neurology November 2020 Volume 77, Number 11

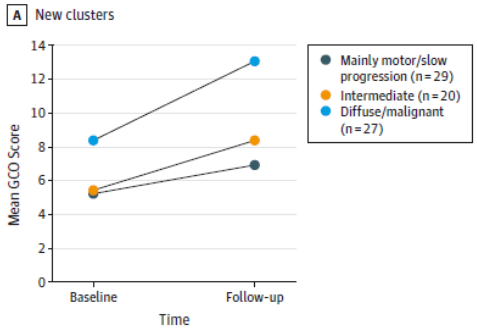
Subtypes of PD - implications for disease progression - and treatment?

Slower/milder

- Younger age
- Genetic +
  - *Parkin, pink-1 -PD*
- Tremor predominant
- Pure Motor

Faster/severe

- Older age
- Akinetic-rigid
- Non-motor predominate
  - Cognitive impairment
  - Autonomic symptoms
  - Lower Body weight ?



Fereshtehnejad et al JAMA Neurol 2017

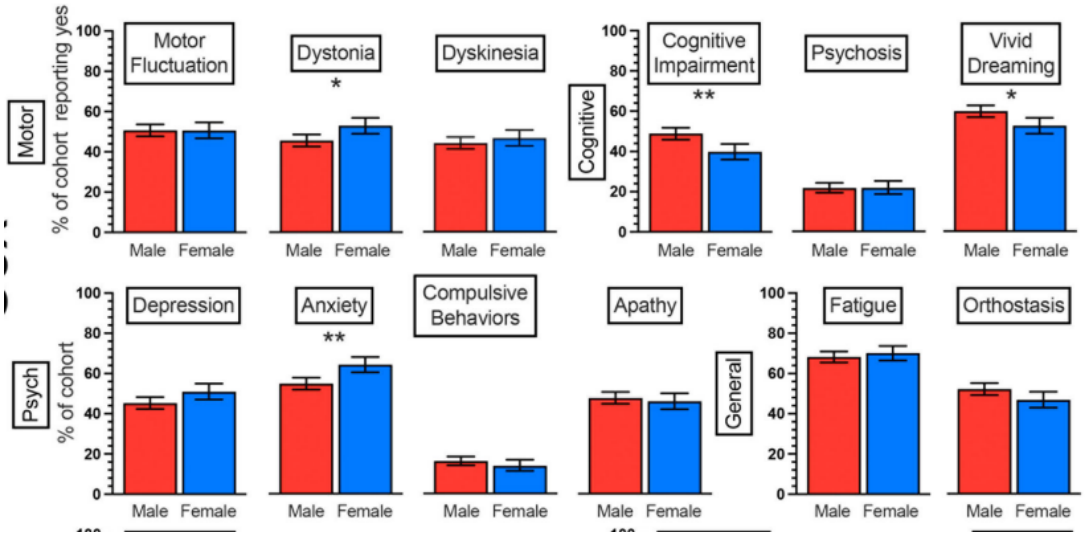
Tremor-dominant PD

- May be less responsive to levodopa
  - high doses can sometime reduce tremor > 1000mg

- Non-dopaminergic targets
  - Anticholinergics (muscarinic M_4)
    - Trihexyphenidyl
  - Serotonergic ($5HT_{2A}$) antagonists (and mixed)
    - Mirtazapine
    - Clozapine
  - Propranolol (esp if Action component)
  - Botulinum Toxin A?
  - Surgery - Thalamic DBS, FUS

Female PD

- Motor Features
  - More dystonia
- Non Motor symptoms
  - More anxiety
  - Less cognitive impairment
  - Less RBD

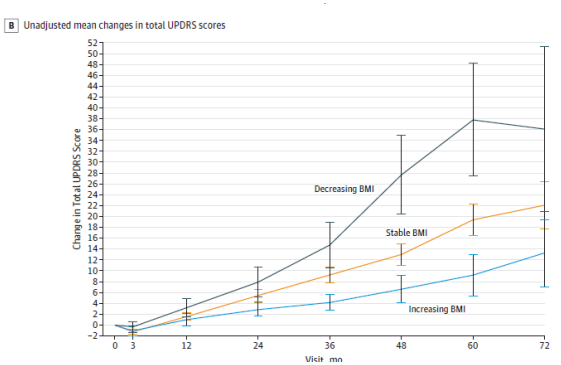


Tropea et al J Parkinson disease 2024

The Thin Parkinson patient

- **Up to 50% of PD unintentional weight loss**
  - "PD related cachexia"

- Lower BMI associated with worse PD symptoms
- Possible reduced survival
- Increased osteoporosis and fractures



Original Investigation

Association Between Change in Body Mass Index, Unified Parkinson's Disease Rating Scale Scores, and Survival Among Persons With Parkinson Disease

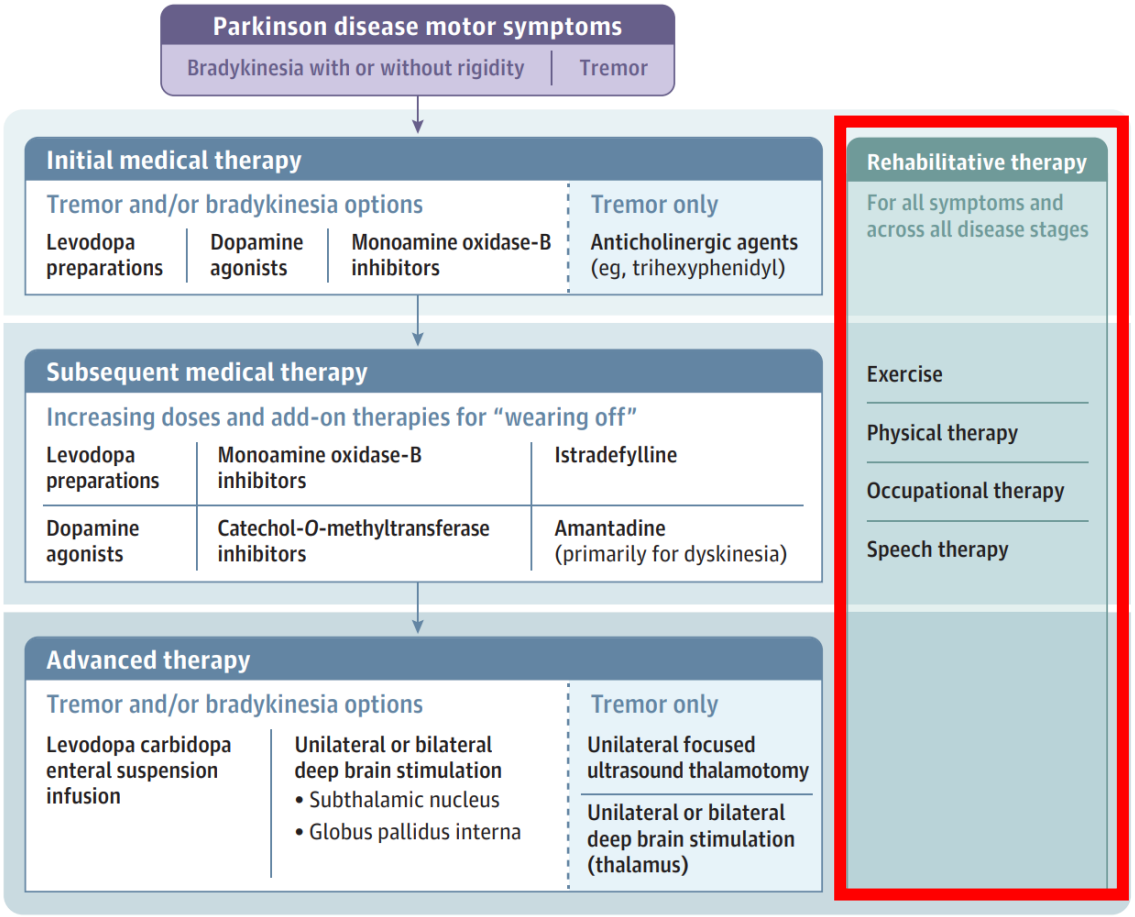
Secondary Analysis of Longitudinal Data From NINDS Exploratory Trials in Parkinson Disease Long-term Study 1

Anne-Marie A. Wills, MD, MPH; Adriana Pérez, PhD; Jue Wang, MS; Xiao Su, BSc; John Morgan, MD; Saja S. Rajan, PhD; Maureen A. Leehey, MD; Gregory M. Pontone, MD; Kelvin L. Chou, MD; Chizoba Umeh, MD; Zoltan Mari, MD; James Boyd, MD; for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators

- **Causes**
  - Reduced calorie intake
    - Anorexia – Anosmia and loss of taste; mood/Constipation
    - Slower eating – dysphagia; bradykinesia
  - Increased loss of calories
    - Tremor/Dyskinesia
  - Pathology
    - Metabolic dysfunction – Hypothalamic; lower leptin /ghrelin
    - ?linked to microbiome = linked to proinflammatory bacteria- muscle and fat metabolism

Exercise, Exercise, Exercise

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



JAMA | Review
Diagnosis and Treatment of Parkinson Di
A Review
Melissa J. Armstrong, MD, MSc; Michael S. Okun, MD
JAMA February 11, 2020 Volume 323, Number 6

Exercise as Medicine in Parkinson Disease ; A Review
Langeskov-Christensen et al JNNP 2024

Which type of exercise should I do?







DANCING WITH PARKINSON'S





Any Exercise is good
"Accessible and Enjoyable and Sweaty if possible"







DANCING WITH PARKINSON'S





Don’t Forget…….

- **Bone** – increased risk of osteoporosis (OR 2.61)
  - Increased risk of fractures (OR 2.28) (Torsney et al JNNP 2014)

- **Skin** – increased (small) risk of melanoma (OR 1.76) (Lee et al Ageing 2022)

- **Driving** - can be controversial/challenging !!
  - Ask the spouse/family



Bonus slides

Diet and supplements

Journal of Parkinson's Disease
1–14
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DOI: 10.1177/1877718X261446386
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Dietary supplements for Parkinson's disease: State of the science

Aakash Prasad[1], Marshal Spenser Shuler[1], Richelle Flanagan[2], Viswas Dayal[3] and Fiona E Lithander[1]

Journal of Parkinson's Disease xx (2023) x–xx
DOI 10.3233/JPD-230264
IOS Press

Review

The Role of Diet in Parkinson's Disease

Kira N. Tosefsky[a,b], Julie Zhu[b], Yolanda N. Wang[a], Joyce S.T. Lam[a], Amanda Cammalleri[a] and Silke Appel-Cresswell[a,c,*]

Parkinson's disease drug therapies in the clinical trial pipeline: 2015–2024

Journal of Parkinson's Disease
1–15
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DOI: 10.1177/1877718X26145154
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Sage | IOS Press

Susan Buff[1], Aleksandra Pilcicka[2], Kenneth Pitzer[3], Brian Fiske[4], Simon RW Stott[2] and Kevin McFarthing[5]

Table 7. PD therapies approved by the FDA between January 1, 2015 and December 31, 2024, listed in descending order of approval date.

Approval year	Therapy	Indication
2024	Vyalev (foscarbidopa/ foslevodopa)	PD motor fluctuations
2024	Crexont (carbidopa/ levodopa)	PD motor fluctuations
2021	Dhivy (carbidopa/ levodopa)	PD motor symptoms
2021	Gocovri (amantadine)	Second FDA approval: PD motor fluctuations
2020	Kynmobi (apomorphine) withdrawn 2023	OFF periods in PD/motor fluctuations
2020	Ongentys (opicapone)	OFF periods in PD/motor fluctuations
2019	Nourianz (istradefylline)	OFF periods in PD/motor fluctuations
2019	Myobloc (rimabotulinumtoxinB)*	Chronic sialorrhea
2018	Inbrija (levodopa inhalation powder)	OFF periods in PD/motor fluctuations
2018	Xeomin (incobotulinumtoxinA)*	Chronic sialorrhea
2018	Osmolex ER (amantadine) withdrawn 2024	Levodopa-induced dyskinesia
2017	Gocovri (amantadine)	First FDA approval: Levodopa-induced dyskinesia
2017	Xadago (safinamide mesylate)	OFF periods in PD/motor fluctuations
2016	Nuplazid (pimavanserin)	Hallucinations and delusions; PD psychosis
2015	Duopa (carbidopa/ levodopa intestinal gel)	PD motor fluctuations
2015	Rytary (carbidopa/ levodopa)	PD motor symptoms

*therapy not specifically approved for PD, but approved for a common non-motor symptom associated with PD.

Experimental Therapeutics in Parkinson's Disease

A Review

Priti Gros, MD[a,b,*,1], Laura Armengou Garcia, MD, PhD[a,1], Susan H. Fox, MD, PhD[a]

Neurol Clin 43 (2025) 399–426

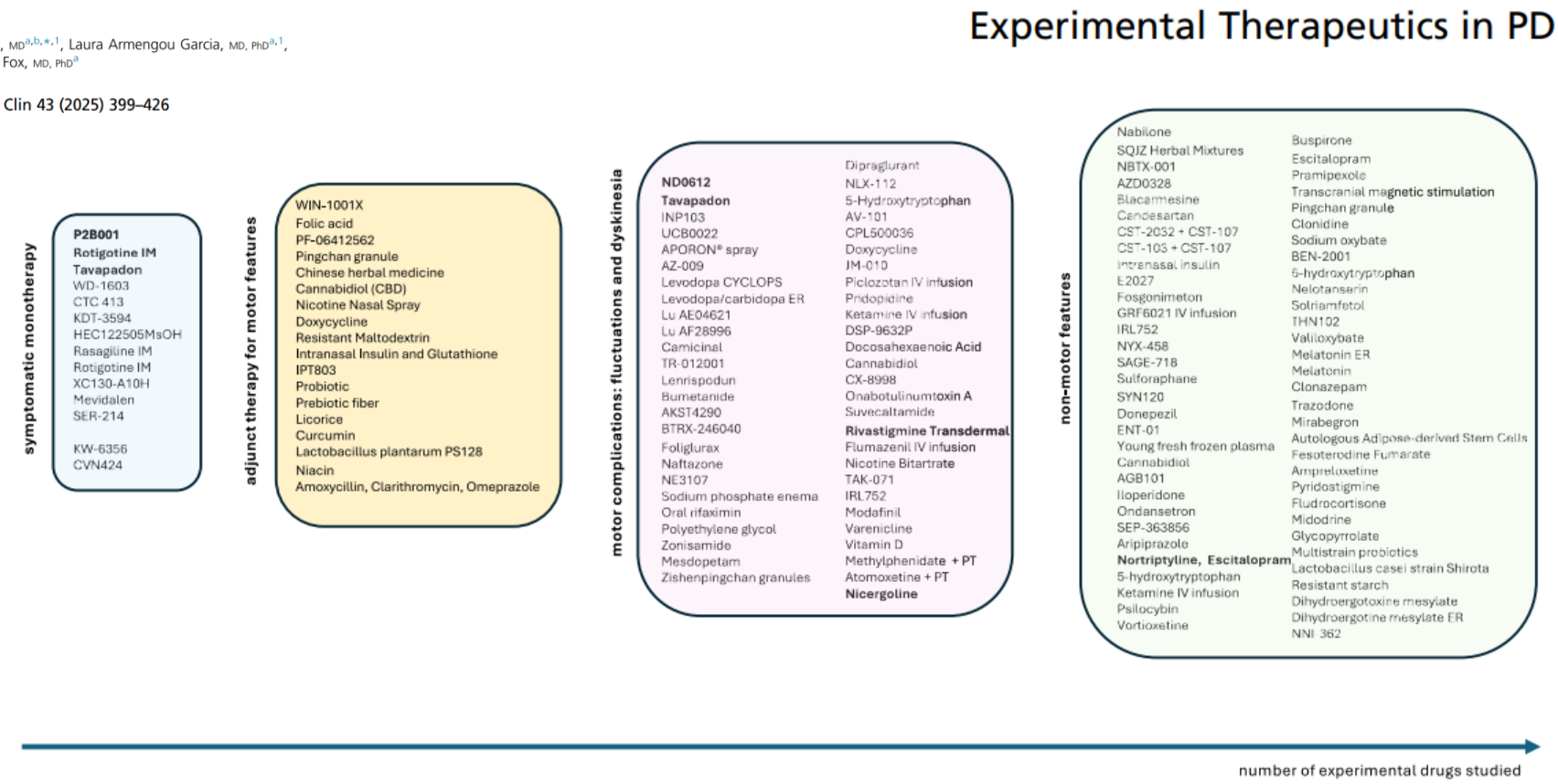


Fig. 1. Overview of experimental drugs studied in the past 5 years for symptomatic treatment of Parkinson's disease. Drugs in phase III trials are in **BOLD**.

PD diagnostic Criteria

Supportive Criteria

1. Clear and dramatic beneficial response to dopaminergic therapy or
2. a) Marked improvement with dose increases or b) marked worsening with dose decreases.
3. Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
4. Presence of levodopa-induced dyskinesia
5. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
6. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Exclusion criteria

1. Unequivocal cerebellar abnormalities,
2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
3. Probable behavioral variant frontotemporal dementia or primary progressive aphasia within 5 y of onset
4. Parkinsonian features restricted to the lower limbs for more than 3 y
5. Treatment with a dopamine receptor blocker/ depleting agent consistent with drug-induced parkinsonism
6. Absence of response to high-dose levodopa *despite at least moderate severity* of disease
7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis, limb ideomotor apraxia, or progressive aphasia
8. Normal functional neuroimaging of the presynaptic dopaminergic system

‘Red Flags’

1. Rapid progression of gait impairment requiring wheelchair within 5 y
2. Absence of progression over 5 y (unless stability is related to treatment)
3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5. Severe autonomic failure in the first 5 y of disease:-
   a) Orthostatic hypotension = decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of other explanation and/or
   b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction

Red Flags *continued*

6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
8. Absence of non-motor features of disease despite 5 y+ duration; ie sleep dysfunction; autonomic dysfunction hyposmia and psychiatric dysfunction
9. Otherwise-unexplained pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
10. Bilateral symmetric parkinsonism; bilateral symptom onset with no side predominance.

Clinical ‘Milestones’ of PD

‘Milestones’ in progression of PD

1. Falls ……
2. Hallucinations
3. Dementia
4. Nursing home care

Once a milestone is reached the time to death is the same – about **4- 5y** *– regardless of age-of-disease onset*

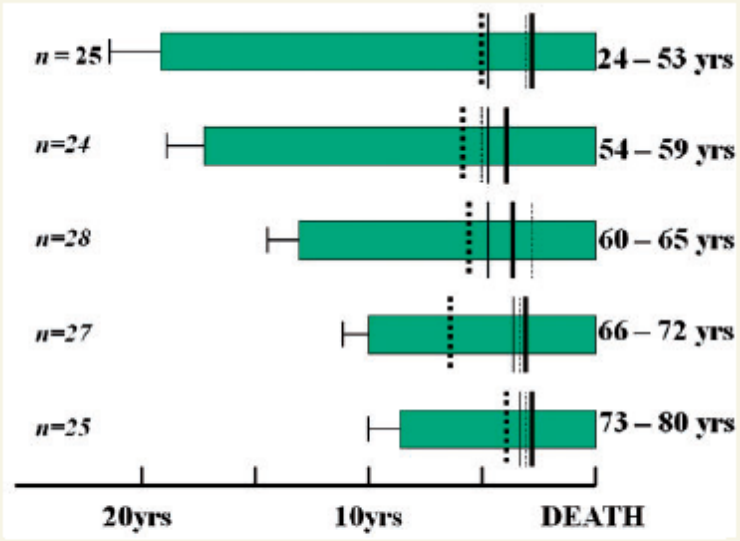


Figure 2 Disease course and disability milestones for five age-at-onset groups. Disease courses aligned for time of death. Same milestone legend as Fig. 1. Error bars show the standard error of the mean disease duration.

Kempster PA, et al Brain 2010

A Review of Levodopa Formulations for the Treatment of Parkinson's Disease Available in the United States

Journal of Pharmacy Practice
2024, Vol. 37(2) 485–494
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DOI: 10.1177/08971900221151194
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Sage

Clare Livingston, PharmD[1], and Laura Monroe-Duprey, PharmD[1]

Table 1. Dosage formulations and pharmacokinetics of levodopa formulations.

Product	Bioavailability	Time to peak concentration for levodopa, hours	Half-Life for levodopa, hours	Doses per day	Available dosage forms
Carbidopa/levodopa IR tablet (Sinemet, Dhivy)	99%	.5 to 2	1.5	3 to 8	Generic tablet: 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg Sinemet: 10 mg/100 mg, 25 mg/100 mg Dhivy: 25 mg/100 mg
Carbidopa/levodopa disintegrating tablet	99%	—	1.5 to 2	3 to 8	Generic tablet: 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg
Carbidopa/levodopa CR tablet (Sinemet CR)	44% to 75%	2	1.5	2 to 3	Generic tablet: 25 mg/100 mg, 50 mg/200 mg
Carbidopa/levodopa ER capsule (Rytary)	70%	1	2	3 to 5	Rytary: 23.75 mg/95 mg, 36.25 mg/145 mg, 48.75 mg/195 mg, 61.25 mg/24 5 mg
Carbidopa/levodopa enteral solution (Duopa)	97%	2.5	1.5	Continuous infusion over 16 hours	Duopa: 4.63 mg/20 mg/mL
Levodopa inhalation powder (Inbrija)	70%	.17 to 2.00	2.3	1 to 5	Inbrija: 42 mg capsule

Subcutaneous Apomorphine infusion

- Toledo study: DBRCT
- 12 weeks
- N = 107
- Primary endpoint; mean reduction in Daily OFF time of + 2.6H v 0.9H placebo
- ON time without troublesome dyskinesia +2.8H v 1.1H placebo
- FDA approved