1

Levodopa-fact and fiction

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2

Objective

- Demystify Levodopa*
  - History
  - Metabolism
  - Case Study
  - Fact vs Fiction
  - Levodopa in clinical practice

* carbidopa/Levodopa (Sinemet®)

3

Levodopa timeline

Carlsson
Hornykiewicz
Cotzias
Yahr
Lloyd

Deficiency of dopamine in brains of PD patients!

- 300 BC: Ayurvedic use of *Mucuna Pruriens*
- 1911, Levodopa synthesized in lab.
- 1940s-60s: Levodopa confirmed to improve mobility in *post-encephalitic parkinsonism*
- 1960s-70s: dopamine and PD linked ; Levodopa improved PD symptoms; *Levodopa approved for PD treatment
- 2000- Carlsson received Nobel Prize
- 2000- present: newer formulations and delivery

1817: Dr. James Parkinson documented clinical symptoms
Late 19th c: Parkinson Disease

*carbidopa/levodopa

Ovallath S, Sulthana B. Levodopa: History and therapeutic applications. Ann Indian Acad Neurol 2017;20:185-9.

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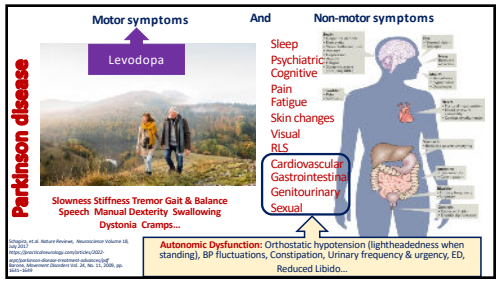
Motor symptoms
And
Non-motor symptoms
Parkinson disease
Levodopa
Slowness Stiffness Tremor Gait & Balance
Speech Manual Dexterity Swallowing
Dystonia Cramps...
Sleep
Psychiatric
Cognitive
Pain
Fatigue
Skin changes
Visual
RLS
Cardiovascular
Gastrointestinal
Genitourinary
Sexual
Autonomic Dysfunction: Orthostatic hypotension (lightheadedness when standing), BP fluctuations, Constipation, Urinary frequency & urgency, ED, Reduced Libido...

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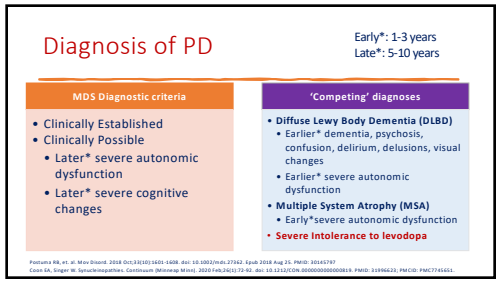
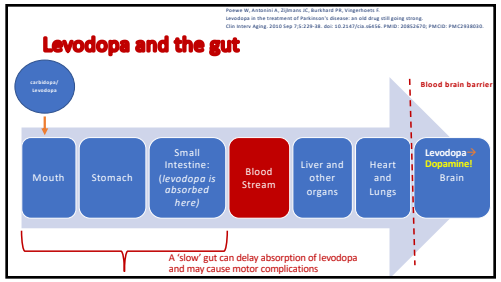
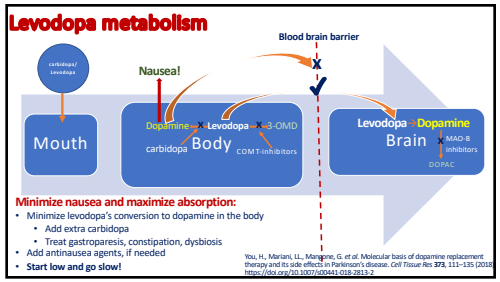

Diagnosis of PD
Early*: 1-3 years
Late*: 5-10 years
MDS Diagnostic criteria
• Clinically Established
• Clinically Possible
• Later* severe autonomic dysfunction
• Later* severe cognitive changes
'Competing' diagnoses
• Diffuse Lewy Body Dementia (DLBD)
• Earlier* dementia, psychosis, confusion, delirium, delusions, visual changes
• Earlier* severe autonomic dysfunction
• Multiple System Atrophy (MSA)
• Early*severe autonomic dysfunction
• Severe Intolerance to levodopa

6


Levodopa and the gut
carbidopa/ Levodopa
Blood brain barrier
Mouth
Stomach
Small Intestine: (levodopa is absorbed here)
Blood Stream
Liver and other organs
Heart and Lungs
Levodopa → Dopamine!
Brain
A 'slow' gut can delay absorption of levodopa and may cause motor complications

7


Levodopa metabolism
Blood brain barrier
carbidopa/ Levodopa
Nausea!
Mouth
Dopamine
Levodopa
3-OMD
carbidopa
Body
COMT-inhibitors
Levodopa → Dopamine
Brain
MAO-B inhibitors
DOPAC
Minimize nausea and maximize absorption:
• Minimize levodopa's conversion to dopamine in the body
• Add extra carbidopa
• Treat gastroparesis, constipation, dysbiosis
• Add antinausea agents, if needed
• Start low and go slow!

8

9

Case Study

- Mr. HW is a 61-year-old man with a six-year history of progressive stiffness and slowness of his L hand, mild disturbance in gait and balance, slightly soft speech, occasional constipation and acting out his dreams. His examination shows parkinsonism, most consistent with Parkinson disease (PD). He is not able to effectively work as a mechanic, the stiffness in his hand is quite bothersome. He is afraid of taking levodopa because 'it might accelerate the progression' of the disease and 'it could be toxic.' He is also concerned about 'premature dyskinesia.' He wants to 'save' the medication for the future. He gets his information from the internet and some support groups he attends.

10

Levodopa is toxic, it accelerates PD

Fiction!

Pathological studies do not show acceleration of cell loss in the brain with chronic levodopa use

Yahr MD, Wolf A, Antunes J-L, Miyoshi K, Duffy P. Autopsy findings in parkinsonism following treatment with levodopa. Neurology. 1972;22(suppl):56-71.

11

Delaying levodopa is a good strategy

Fiction!

Several studies have shown that earlier treatment with levodopa

- Reduces long-term disability
- Reduces mortality compared to untreated groups
- Overall improves quality of life

Levodopa-phobia worsens quality of life

Diamond, S. G., Markham, C. H., Hoehn, M. M., McDowell, F. H., & Muenter, M. D. (1987). *Multi-center study of Parkinson mortality with early versus later dopa treatment. Annals of Neurology, 22*(1), 8–12. doi:10.1002/ana.410220105

Rajput AH, Uitti RJ, Rajput AH, Offord KP. **Timely levodopa (LD) administration prolongs survival in Parkinson's disease**. Parkinsonism Relat Disord. 1997 Nov;3(3):159-65. doi: 10.1016/S1353-8020(97)00030-8. PMID: 18591070.

Horstink R. "Levodopa-phobia": a new iatrogenic cause of disability in Parkinson's disease. Neurology. 2005;64(5):922-924.

12

’Saving’ levodopa for later results in less usage

Fiction!

The dose of levodopa needed for treatment depends on duration of the disease & individual needs, not when the medicine is started

Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021 Jun 12;397(10291):2284-2303. doi: 10.1016/S0140-6736(21)00218-X. Epub 2021 Apr 10. PMID: 33848468.

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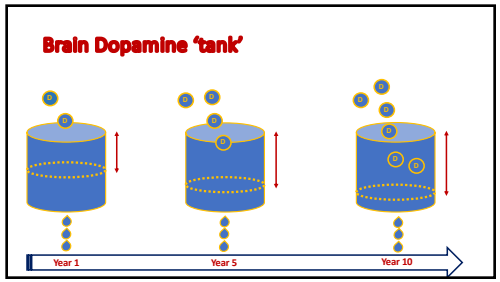


14

Levodopa becomes ineffective down the road

- Fiction!
- Levodopa retains its efficacy throughout, however, the duration of response shortens
- Duration of each individual dose reflects extent of dopamine cell loss
- *Is the diagnosis of PD secure?**

Ahlskog JE. Common Myths and Misconceptions That Sidetrack Parkinson Disease Treatment, to the Detriment of Patients. Mayo Clin Proc. 2020 Oct;95(10):2225-2234. doi: 10.1016/j.mayocp.2020.02.006. PMID: 33012351.
*https://www.apdaparkinson.org/wp-content/uploads/2021/12/NW-ParkinsonPathfinder_Winter21_Web-1.pdf

15

Levodopa accelerates dyskinesia…

- Fiction!
- Dyskinesia:
  - Duration of disease & age of onset
  - Dose of Levodopa, not when it is started
    - Lowering dose eliminates dyskinesia
- Dyskinesia is inevitable in 60% to 80% of PD within 10 years
- Not all dyskinesia is bothersome
  - Dyskinesia can be effectively managed

Van Gerpen JA, Kumar N, Bower JH, Wiegand S, Ahlskog JE. Levodopa-associated dyskinesia risk among Parkinson disease patients in Olmsted County, Minnesota, 1976-1990. Arch Neurol. 2006 Feb;63(2):205-9. doi: 10.1001/archneur.63.2.205. PMID: 16476808.
Kwon DK, Kwatra M, Wang J, Ko HS. Levodopa-Induced Dyskinesia in Parkinson's Disease: Pathogenesis and Emerging Treatment Strategies. Cells. 2022 Nov 23;11(23):3736. doi: 10.3390/cells11233736. PMID: 36496996; PMCID: PMC9736114.

16

17

Levodopa may not work well in some individuals

- Fact! 8-10% of PD patients do not respond adequately
  - *Pseudoresistance* to levodopa:
    - Inadequate dose
    - Intolerance
    - Slow gut: poor absroption
    - Levodopa 'blockers'
  - Not all motor symptoms respond equally in everyone
  - Mixed response in older individuals
  - *Is the diagnosis of PD secure?**

Nonnekes J, Timmer MH, de Vries NM, Rascol O, Helmich RC, Bloem BR. Unmasking levodopa resistance in Parkinson's disease. Mov Disord. 2016 Nov;31(11):1602-1609. doi: 10.1002/mds.26712. Epub 2016 Jul 19. PMID: 27430479.

**https://www.apdaparkinson.org/wp-content/uploads/2021/12/NW-ParkinsonPathfinder_Winter21_Web-1.pdf*

18

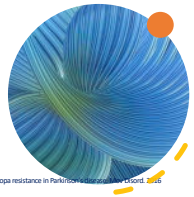
Levodopa *Pseudoresistance*

Inadequate dose:

- >600 mg/day to 1200 mg/day before declaring levodopa failure

Intolerance*:

- GI symptoms: nausea, bloating
- Orthostatic hypotension (dizziness)
- Psychosis, confusion, delirium



Nonnekes J, Timmer MH, de Vries NM, Rascol O, Helmich RC, Bloem BR. Unmasking levodopa resistance in Parkinson's disease. Mov Disord. 2016 Nov;31(11):1602-1609. doi: 10.1002/mds.26712. Epub 2016 Jul 19. PMID: 27430479.

*APDA article on levodopa intolerance, Pathfinder Summer 2023, Feb 16: GI symptoms in PD

19

Levodopa Intolerance*

Sleepiness, fatigue, behavioral changes…

Non-motor side-effects	Nonpharmacological Management	Pharmacological Treatment:
Gastrointestinal	• Dietary modification • Ginger products • Taking levodopa with non-proteinaceous food	• Start low and go slow • Primary care, nutritionist, and GI evaluation • OTC products to treat constipation, bloating & dysbiosis: bowel regimen, probiotics, fermented foods • Carbidopa, COMT-inhibitors, ondansetron, domperidone, pyridostigmine, linaclotide, lubiprostone
Orthostatic hypotension	• Hydration and salting • Compression garments • Avoiding hot environments • Small frequent meals • Fall precautions	• Safely eliminating other medicines that can cause OH • Pyridostigmine, droxidopa, fludrocortisone, midodrine • Cardiovascular consultation for persistent OH
Psychiatric and cognitive: Advanced PD	• Patient and caregiver safety	• Elimination of medications that exacerbate psychosis • Adjustment of levodopa dose • Psychiatric and psychological consultation • Pimavaserin, quetiapine, rivastigmine, donepezil, clozapine

Abhishek Lenka, Gianluca Di Maria, Guillaume Lamotte, Laxman Bahroo & Joseph Jankovic (2022) Practical pearls to improve the efficacy and tolerability of levodopa in Parkinson's disease, Expert Review of Neurotherapeutics, 22:6, 469-498, DOI: 10.1080/14737175.2022.2091436

*APDA article on levodopa intolerance, Pathfinder Summer 2023, Feb 16: GI symptoms in PD

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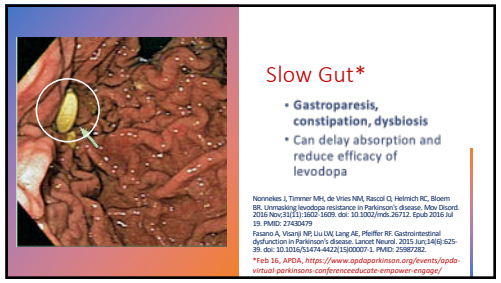

Slow Gut*

- **Gastroparesis, constipation, dysbiosis**
- Can delay absorption and reduce efficacy of levodopa

Nonnekes J, Timmer MH, de Vries NM, Rascol O, Helmich RC, Bloem BR. Unmasking levodopa resistance in Parkinson's disease. Mov Disord. 2016 Nov;31(11):1602-1609. doi: 10.1002/mds.26712. Epub 2016 Jul 19. PMID: 27430479

Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol. 2015 Jun;14(6):625-39. doi: 10.1016/S1474-4422(15)00007-1. PMID: 25987282.

*Feb 16, APDA, *https://www.apdaparkinson.org/events/apda-virtual-parkinsons-conferenceeducate-empower-engage/*

21

Levodopa Blockers

Protein:

- Try to take levodopa 30 minutes before a meal

Medications:

- High doses of B6
- Iron salts
- Antipsychotics, antiepileptics, cardiovascular, antidepressants, antinausea, Metoclopramide, cancer drugs, anesthetics, Flunarizine, Cinnarizine…

Ahlskog JE. Common Myths and Misconceptions That Sidetrack Parkinson Disease Treatment, to the Detriment of Patients. Mayo Clin Proc. 2020 Oct;95(10):2225-2234. doi: 10.1016/j.mayocp.2020.02.006. PMID: 33012351.

Feldman M, Marmol S, Margolesky J. Updated Perspectives on the Management of Drug-Induced Parkinsonism (DIP): Insights from the Clinic. Ther Clin Risk Manag. 2022 Dec 20;18:1129-1142. doi: 10.2147/TCRM.S360268. PMID: 36573102; PMCID: PMC9789682.

22

Motor* symptoms responsive to levodopa

- Bradykinesia or slowness
- Stiffness
- Tremor — Upto 1/3rd of PD tremor may not respond adequately
- Gait and balance
- Manual dexterity
- Speech and Swallowing

*Levodopa is not indicated for treatment of **nonmotor** symptoms

Nonnekes J, Timmer MH, de Vries NM, Rascol O, Helmich RC, Bloem BR. Unmasking levodopa resistance in Parkinson's disease. Mov Disord. 2016 Nov;31(11):1602-1609. doi: 10.1002/mds.26712. Epub 2016 Jul 19. PMID: 27430479

23

Levodopa responsiveness in older individuals

- 'Mixed' Brain Pathology due to coexisting:
  - Alzheimer's disease
  - Vascular disease
  - Normal pressure hydrocephalus
  - Late onset genetic mutations (TDP-43)

Buchman AS, Yu L, Wilson RS, Leurgans SE, Nag S, Shulman JM, Barnes LL, Schneider JA, Bennett DA. Progressive parkinsonism in older adults is related to the burden of mixed brain pathologies. Neurology. 2019 Apr 16;92(16):e1821-e1830. doi: 10.1212/WNL.0000000000007315. Epub 2019 Mar 20. PMID: 30894446; PMCID: PMC6550497.

Nonnekes J, Timmer MH, de Vries NM, Rascol O, Helmich RC, Bloem BR. Unmasking levodopa resistance in Parkinson's disease. Mov Disord. 2016 Nov;31(11):1602-1609. doi: 10.1002/mds.26712. Epub 2016 Jul 19. PMID: 27430479

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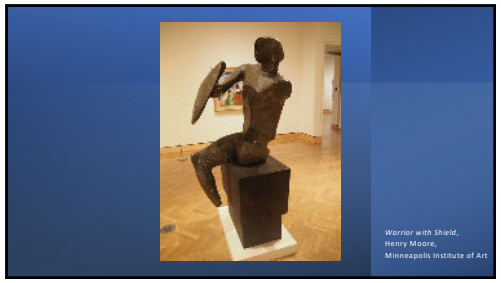


25

Levodopa formulations

Oral

- carbdiopa/Levodopa 25/100 (Sinemet® 25/100)
- Sinemet®25/100 CR
- carbidopa/Levodopa 10/100 (Parcopa®--sublingual-'rescue' bypasses the stomach only)
- Sinemet® 50/200 CR (nighttime use)
- ~~Sinemet® 25/250~~
- (Carbidopa and Levodopa) Extended-Release capsules [Rytary™]
  - /95, /145, /195, /245

https://practicalneurology.com/articles/2022-sept/parkinson-disease-treatment-advances/pdf

26

Levodopa formulations

Oral

- Levodopa Inhalation Powder 42 mg capsules (Inbrija® - 'rescue' drug)

Infusion

- carbidopa/levodopa enteral suspension 4.63 mg/ 20 mg per ml (Duopa™)

https://practicalneurology.com/articles/2022-sept/parkinson-disease-treatmentedvances/pdf
https://www.duopa.com

27

What about other medications?

Dopamine Agonists	Sleepiness, Sudden sleep attacks, Weight gain, Lightheadedness, Leg Swelling, Psychosis, Impulse Control Disorders: overeating, hoarding, excessive shopping, hypersexuality, gambling
MOA B inhibitors	Adjunct medications
COMT inhibitors	
Amantadine formulations	
Istradefylline	
Apomorphine	
Safinamide	

https://practicalneurology.com/articles/2022-sept/parkinson-disease-treatment-advances/pdf
Ahlskog JE. Common Myths and Misconceptions That Sidetrack Parkinson Disease Treatment, to the Detriment of Patients. Mayo Clin Proc. 2020 Oct;95(10):2225-2234. doi: 10.1016/j.mayocp.2020.02.006. PMID: 33012351.

28

Flight of Night, Paul Manship

Minneapolis Institute of Art

29

Case study

Mr. HW was given pramipexole which caused leg swelling and dizziness; rotigotine patch caused skin rash; rasagiline only minimally improved symptoms. He was educated about the benefits of levodopa in PD.

carbidopa/levodopa 25/100 was initiated and gradually increased to 600 mg/day in divided doses: significant & sustained improvement of slowness, stiffness, speed of walking. QOL improved. He was able to practice his trade

30

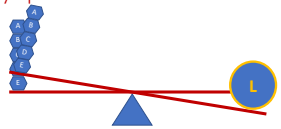
Case study: Multidisciplinary treatment

Low dose melatonin reduced dream enacting	Dietary changes and daily sensible exercise improved constipation and physical endurance	Dermatological exam identified basal cell cancer which was treated
LSVT improved speech	Eye exam, colonoscopies, immunizations and primary care was up to date	Overall QOL improved and he was able to effectively work as a mechanic

Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021 Jun 12;397(10291):2284-2303. doi: 10.1016/S0140-6736(21)00218-X. Epub 2021 Apr 10. PMID: 33848468.

31

Levodopa is the gold standard for treating PD motor symptoms



L: carbidopa/levodopa

A, B, C, D, E: Other PD medications

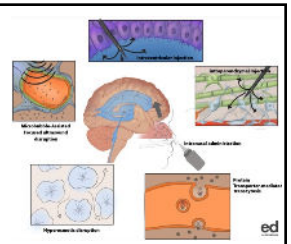
Ahlskog JE. Common Myths and Misconceptions That Sidetrack Parkinson Disease Treatment, to the Detriment of Patients. Mayo Clin Proc. 2020 Oct;95(10):2225-2234. doi: 10.1016/j.mayocp.2020.02.006. PMID: 33012351.

PD Med Collaborative Group; Gray R, Ives N, Rick C, Patel S, Gray A, Jenkinson C, McIntosh E, Wheatley K, Williams A, Clarke CE. 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. Lancet. 2014 Sep 27;384(9949):1196-205. doi: 10.1016/S0140-6736(14)60683-8. Epub 2014 Jun 11. Erratum in: Lancet. 2014 Sep 27;384(9949):1184. PMID: 24928805.

32

Levodopa delivery systems-the future

- Pro-drugs
- Subcutaneous infusion of foslevodopa/foscarbidopa
- Transnasal
- Intravenous
- Transcutaneous
- Intracerebral



Ndemazie, N.B., Inkoom, A., Morfaw, E.F. *et al.* Multi-disciplinary Approach for Drug and Gene Delivery Systems to the Brain. *AAPS PharmSciTech* **23**, 11 (2022). https://doi.org/10.1208/s12249-021-02144-1

33

VIEWPOINT

Levodopa Is the Best Symptomatic Therapy for PD: Nothing More, Nothing Less!

C. Warren Olanow, MD, FRCPC, FRCP(London)*

Olanow CW. Levodopa is the best symptomatic therapy for PD: Nothing more, nothing less. Mov Disord. 2019 Jun;34(6):812-815. doi: 10.1002/mds.27690. Epub 2019 Apr 16. PMID: 30990922.

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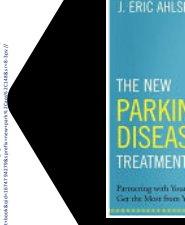

Caveat: doesn't include newer levodopa formulations, adjunct medications for PD

35