10 Common Questions about Parkinson Medications

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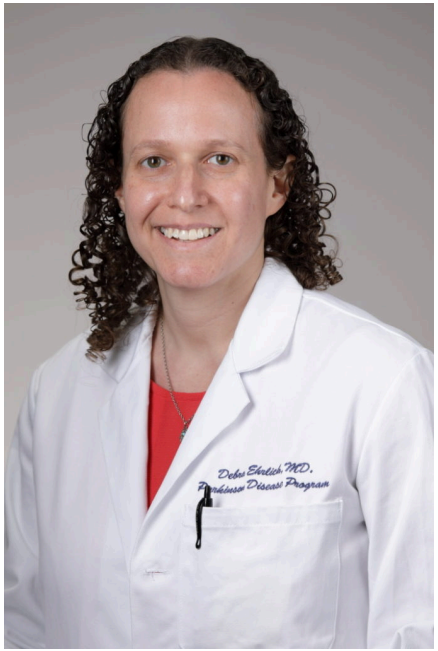

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10 Common Questions

1. When is the right time to start treatment for Parkinson's Disease?
2. Can what I eat effect how well my medications work?
3. Which form of levodopa is right for me?
4. What is the difference between IR vs ER vs CR forms of levodopa?
5. Will levodopa stop working?
6. Are dopamine agonists safe?
7. How can I reduce dyskinesia?
8. How can I reduce my OFF time?
9. Are there any newly approved medications for PD?
10. What medications are in clinical trials?

Learning Objectives

- Understand the different formulations of levodopa
- Learn about medication strategies to reduce dyskinesia and/or OFF time
- Discuss newly approved medications for Parkinson's Disease and potential new treatments in clinical trials

When is the right time to start treatment for Parkinson's Disease?

- The right time to start medication to treat PD may vary from person to person.

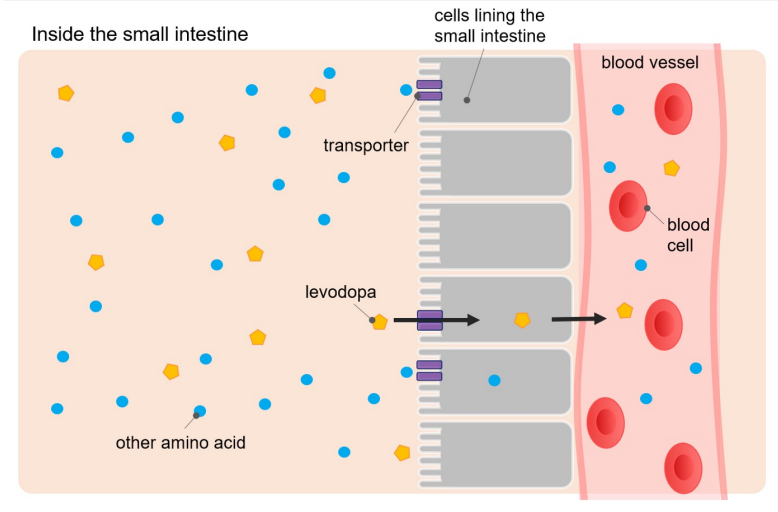
- Some important considerations can help guide the decision:
  - -Do symptoms interfere with work or daily activities
  - -Is balance impaired?
  - -Do symptoms impact social functioning?
  - -Can symptoms cause increased risk of harm?

Can what I eat effect how well my medications work?

- Yes, dietary protein can interfere with absorption of levodopa
- However, this only affects a minority of people treated with levodopa

Can what I eat effect how well my medications work?

- **<u>The protein effect</u>**
- When a tablet of levodopa is swallowed, it travels through the digestive system
- Levodopa must be absorbed in the small intestine in order to enter the bloodstream, where it then travels to the brain where it exerts its effects
- Transporter cells line the small intestine and transport proteins from the small intestine across the cell lining and into the bloodstream
- Levodopa and other proteins use the same transporters
- Large amounts of protein from food may interfere with the transport of levodopa



https://medium.com/parkinsons-uk/parkinsons-and-protein-what-s-the-connection-41e6c820e071

Can what I eat effect how well my medications work?

- If you do not notice any significant differences in medication effects after large or protein rich meals, then no need to worry about this
- If you do notice that your medication doesn't work as well after large or protein rich meals, some adjustments may be helpful:
  - -Take levodopa >30 minutes before or >60 minutes after meals
  - -Eat the majority of your protein at times of the day when you are less active
  - -Try eating smaller quantities more frequently

Which form of levodopa is right for me?

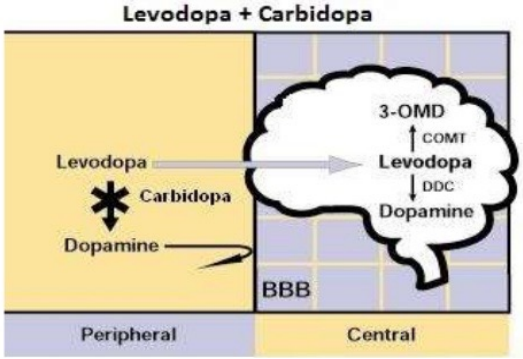
What is levodopa?

- Used to treat symptoms of Parkinson's Disease since the late 1960s
- In Parkinson's Disease, the brain cells (neurons) which produce dopamine stop functioning
- The lack of dopamine in the brain causes problems with movement and other functions
- The chemical structure of dopamine makes it unable to cross the protective blood-brain-barrier, however, levodopa is able to freely enter the brain
- Once in the brain, levodopa is absorbed by neurons which convert it to dopamine

Which form of levodopa is right for me?

What is carbidopa?

- When levodopa is converted to dopamine in the gut, it can result in nausea
- Carbidopa prevents levodopa from being converted to dopamine outside of the brain
- This reduces the risk for nausea and allows more levodopa to get to the brain
- In Canada and Europe, a similar agent called benserazide is used



Which form of levodopa is right for me?

Generic name	Trade/Brand Name	Important information
Carbidopa/levodopa immediate release (IR)	Sinemet	Available in 3 doses 10/100, 25/100, 25/250
Carbidopa/levodopa dissolvable	Parcopa	Tablet that dissolves on the tongue
Carbidopa/levodopa fractionated	Dhivy	Scored tablet, can easily break into 25mg segments
Carbidopa/levodopa extended/controlled release (ER/CR)	Sinemet CR	Controlled release/extended-release tablet Does not always give reliable response
Carbidopa/levodopa extended- release capsules	Rytary	Extended-release capsule contains microbeads that are dissolved in the stomach at different speeds, resulting in absorption over longer period of time
Carbidopa/levodopa intestinal gel	Duopa (US); Duodopa (Canada, Europe)	Intestinal gel form infused through a portable pump to a surgically implanted tube in small intestine, bypasses the stomach
Inhalable levodopa	Inbrija	Inhaled, absorbed through lungs, works quicker than pills, add-on medication only to treat OFF times (up to 5x/day)

What is the difference between immediate release and extended-release levodopa?

- Immediate release levodopa is considered the goal standard for treatment of symptoms of PD
- Different formulations of levodopa/carbidopa are absorbed differently by the body
- Because CR/ER formulations are designed to release slowly, less functional dose is available at any given time compared to immediate release
- The **levodopa equivalent dose** is a calculation that enables comparison of other PD medications to levodopa/carbidopa IR
- 100mg dose of each is equivalent to:

  -CD/LD IR 100mg = C/L CR 75mg = Rytary 50-60mg

TABLE 1 *Conversion factors for calculating total LED for commonly used agents*

Drug Class	Drug (*D*)	Conversion Factor/Ratio	Example	Calculated LED of the Example
L-dopa	IR L-dopa	DD × 1	100 mg *D* tid	300 mg
	CR L-dopa	DD × 0.75	100 mg *D* qd	75 mg
	ER L-dopa	DD × 0.5[c]	200 mg *D* tid	300 mg
	Duodopa	DD × 1.11	7-mL bolus +4.7 mL/h for 16 hours = 1,644 mg/day	1,825 mg

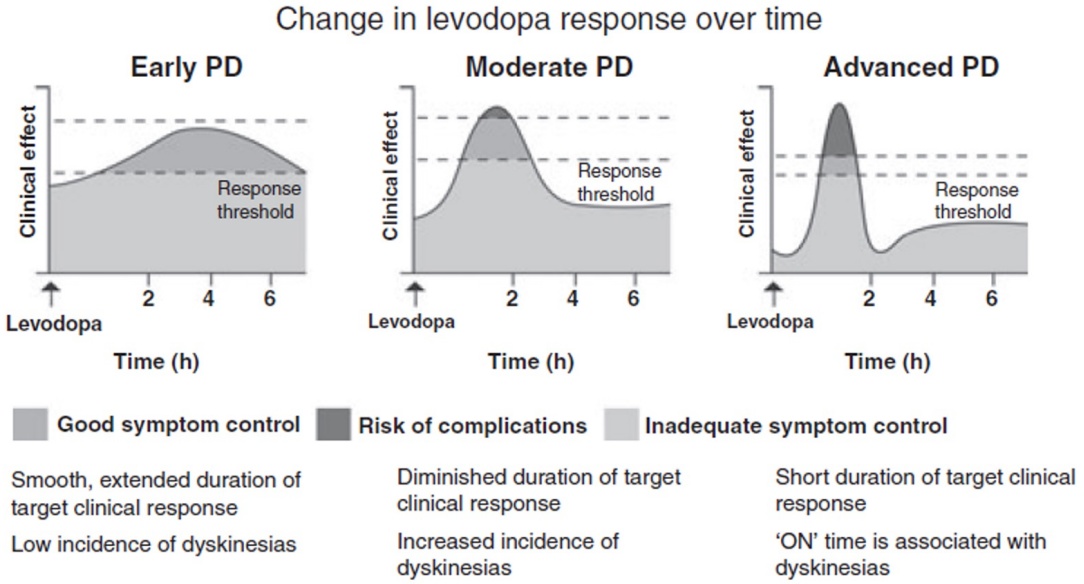
Schade S, et al, Mov Dis Clin Pract, 2020; 7(3) 343-345

Will levodopa stop working?

No, levodopa will not stop working

- Levodopa effectively treats many symptoms, though is not a cure for PD
- Parkinson's symptoms will slowly progress over time. Motor symptoms will gradually worsen, though will continue to benefit from treatment with carbidopa/levodopa
- In early years of PD, long-duration response to levodopa
- Response to levodopa becomes shorter as disease progresses, resulting in the need to take medication more frequently
- Some motor symptoms may not be due to the lack of dopamine, therefore, will not be improved by increasing dopamine in the brain

Will levodopa stop working?



Schapira AH, Emre M, Jenner P, Poewe W. Levodopa in the treatment of Parkinson's disease. Eur J Neurol. 2009;16:982-989.

Are dopamine agonists safe?

- Dopamine agonists are a group of medications that mimic the effects of dopamine
- Stimulate dopamine receptors in the brain
- They can be taken alone or combined with other PD medications

Generic name	Trade name	Important information
Pramipexole	Mirapex	Usually dosed 3x per day
Pramipexole ER	Mirapex ER	Usually dosed 1-2x per day
Ropinirole	Requip	Usually dosed 3x per day
Ropinirole extended release (XL)	Requip XL	Usually dosed 1-2x per day
Rotigotine	Neupro	Transdermal patch, delivers medication through the skin directly to bloodstream, bypasses stomach
Apomorphine subcutaneous	Apokyn	Injected under skin, quick onset of action, used as rescue for OFF time, must be started with anti-nausea medication
Apomorphine sublingual	Kynmobi	Sublingual film, dissolves when placed under the tongue, used to treat OFF time

Are dopamine agonists safe?

Important side effects associated with dopamine agonists:

- Impulse control disorders:
  - -Compulsive gambling, excessive shopping, hypersexuality, compulsive behaviors (repetitive somewhat purposeless activities like organized, sorting or collecting, hobbyism)
  - -More common if younger, longer disease duration, higher or more frequent dosing, male, history of gambling or compulsive behaviors
- Sleep attacks
  - -Fall asleep suddenly, without warning

Are dopamine agonists safe?

Benefits of dopamine agonists

- Improve motor symptoms of PD
- Effects last longer than levodopa
- May be less likely to lead to dyskinesia or OFF fluctuation
- Do not compete with protein for absorption, no dietary restrictions

Are dopamine agonists safe?

Answer:

- Dopamine agonists can be a safe and effective treatment for many individuals, though there are some important risks which must be considered.
- The potential benefits and risks should be discussed with your doctor.

How can I reduce dyskinesia?

Dyskinesia

- Involuntary movements
- Movements can be erratic, writhing, jerking, or spasms
- Usually most prominent on most affected side of the body
- Occur as a side-effect from some Parkinson's medications, though underlying cause is not completely known
- May be mild or non-bothersome, can be severe

Two types of dyskinesia

- **Peak dose dyskinesia**
  - -Most common type
  - -Occurs when the concentration of levodopa in the blood is at its highest
  - -Usually the same time when medications having best effects to control symptoms
- **Diphasic dyskinesia**
  - -Occurs as medications are beginning to work and beginning to wear off

How can I reduce dyskinesia?

- Who is at greatest risk of dyskinesia?
  - -Younger age of onset (<60)
  - -Higher doses of levodopa
  - -Longer disease duration
  - -female
- Some patients will never develop dyskinesia

How can I reduce dyskinesia?

Strategies to reduce dyskinesia

- Mild/non-bothersome dyskinesia does not need to be treated
- Mild PD symptoms could be treated with non-levodopa agents or use combination therapies to reduce the levodopa dose
- Medication adjustment
  - -Peak dose dyskinesia: reduce levodopa dose (if tolerated)
  - -Diphasic dyskinesia: reduce OFF time by using longer acting formulations or additional medications
  - -Add Amantadine (amantadine, Symmetrel, Gocovri, Osmolex ER)
- Deep brain stimulation
- Reduce stress

How can I reduce my OFF time?

What is OFF time?

- Time when symptoms return between medication doses
- Most common in more advanced disease
- May come on suddenly or gradually
- May be predictable or unpredictable
- Can occur before first dose of medication or between doses

How can I reduce my OFF time?

- Take your medication on a schedule (consider setting an alarm)
- Separate timing of medications from meals
- Talk to your doctor about your off time
- Keeping a log of your off time can help your doctor notice trends
- Increase frequency or dose of medications
- Take longer acting medications
- Add medications that can help reduce OFF time (COMT inhibitors, adenosine receptor antagonist, MAO-B inhibitors
- OFF ”rescue” medications: Inbrijia, apomorphine

Are there any newly approved medications for PD?

Fractionated carbidopa/levodopa (Dhivy)

- FDA approved in November 2021
- Immediate release carbidopa/levodopa 25/100mg tablet
- Similar to other available IR carbidopa/levodopa (e.g. Sinemet IR)
- Scored tablet with 4 fractionated segments
- Each segment contains 6.25/25mg
- This may enable smaller and more specific levodopa doses
- May be helpful in those who have difficulty with cutting a pill
- Side effects similar to other levodopa formulations

DHIVY is a 25/100-mg IR tablet of CD/LD[1]

Scored with 4 fractionated segments[1]

Each segment contains 6.25/25 mg[1]

Are there any newly approved medications for PD?

Apomorphine sublingual film (Kynmobi)

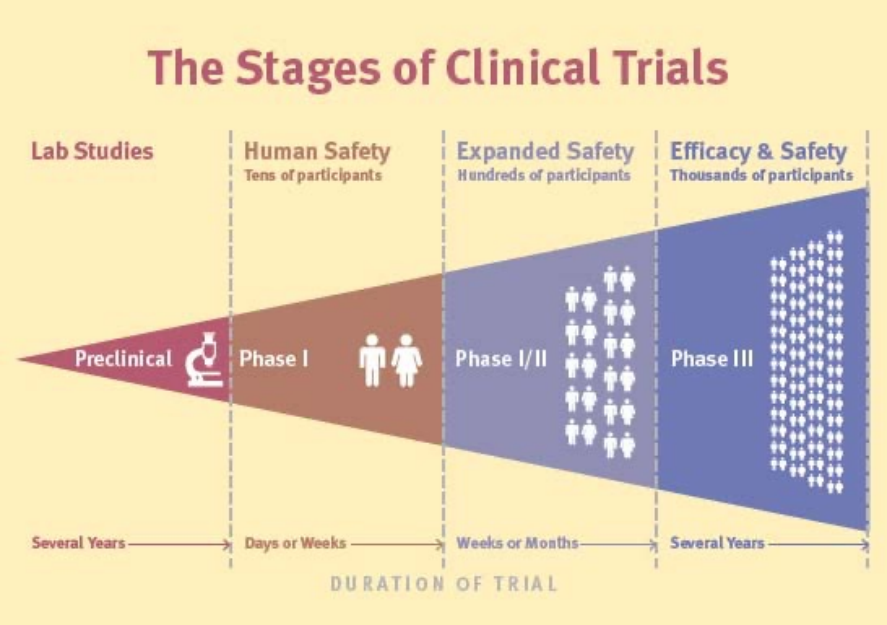
- FDA approved May 2020
- Sublingual film (film that is placed under the tongue)
- Dopamine agonist
- Taken as needed when symptoms of an off episode start
- Doses taken at least 2 hours apart up to 5 times per day
- First dose usually taken in doctor's office (monitor heart rate and blood pressure)
- Common side effects: tongue soreness or swelling, nausea, sleepiness, or dizziness
- An antinausea medication usually given with this for the first few months

Are there any newly approved medications for PD?

Gocovri (amantadine extended release)

- FDA approved for 2 indications in treatment of PD
  - -2017 FDA approved for treatment of dyskinesia in PD
  - -2021 FDA approved as adjunctive treatment to levodopa/carbidopa in PD patient's experiencing OFF episodes
- Taken once daily at bedtime
- Side effects similar to other formulations of amantadine

What medications are in clinical trials?

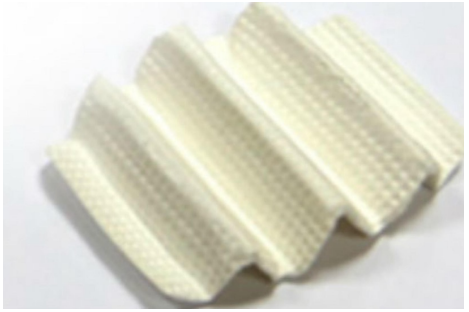


Brainandlife.org

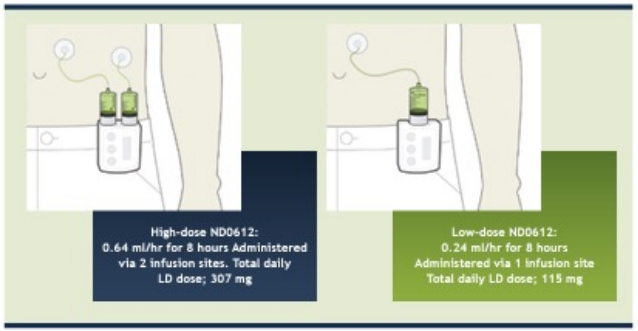
What medications are in clinical trials?

Levodopa delivery

- Accordion Pill (AP-CD/LD)-Phase 3 (Intec Pharma)
  -multilayered pill designed to release slowly from the stomach
  -improved absorption and more stable levodopa doses in the blood



- Subcutaneous carbidopa/levodopa-ND0612 (Neuroderm pump/pump-patch) Phase 3
  -Liquid formulation of carbidopa/levodopa that enables subcutaneous administration
  -Continuous administration over 24hrs/day with an infusion pump via 1 or 2 infusion sites



What medications are in clinical trials?

Disease Modifying Treatments: Drug repurposing

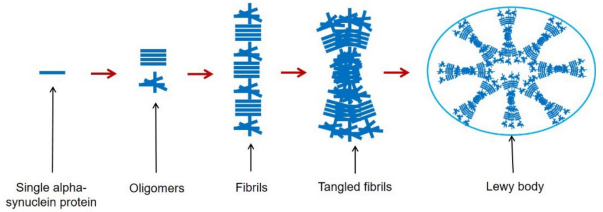
- Exanatide
  - -FDA approved injectable medication used to treat diabetes
  - -Preclinical studies show potential neuroprotective effects
  - -Phase 2 randomized, double-blind, placebo-controlled study
  - -Positive effects on practically defined off-medication scores in Parkinson's disease, which were sustained beyond the period of exposure
- Isradipine
  - -FDA approved drug used to treat high blood pressure
  - -May have protective effects on brain cells
  - -Compared to placebo, isradipine 5mg twice daily over 36 months did not slow PD progression
- Inosine
  - -Nutritional supplement that raises urate (antioxidant) levels
  - -Lab studies show urate protects brain cells
  - -Epidemiological/population studies show association between higher levels of urate and lower PD risk and slower disease progression in people with PD
  - -SURE-PD3 phase 3 trial ended early because preliminary results indicated the study would not be able to show slowing of disease progression

What medications are in clinical trials?

Disease modifying: Alpha-synuclein

Alpha synuclein is a protein that is normally found in the body, though its exact function is not known.
Lewy bodies are clumps of protein made of up abnormally clumped alpha-synuclein found in the brains of people with Parkinson disease

- BIIB054 (Biogen antibody): Aims to prevent alpha synuclein from spreading (SPARK study-phase 2)
  - Study discontinued, failed to meat goals for improvement in symptoms
- RO7046015 (Protena/Roche): Antibody aims to prevent alpha synuclein from spreading (phase 2)



From a single protein to a Lewy body

What medications are in clinical trials?

Disease Modifying: Genetic targets

- GBA gene: mutations in the GBA gene are associated with PD and linked to dysfunction of cells
  - -Venglustat (Sanofi Genzyme): drug reduces accumulation of lipids (fats) that build up in cells and cause cellular dysfunction in people with GBA mutations
    - -MOVES-PD phase 2 study failed to meet is primary endpoint and did not show improvement in UPDRS parts 2 or 3—study discontinued
  - -LTI-291 (Lysosomal Therapeutics/BIAL): activates glucocerebrosides and enhances its activity
    - -Phase 2 trial is underway
- LRRK2 gene: most frequent cause of inherited PD and risk variant in sporadic PD
  - -DNL201 (Denali): LRRK2 inhibitor
    - -Phase 1 studies demonstrated tolerability and target engagement
  - -BIIB122/DNL151(Biogen/Denali): LRRK2 inhibitor
    - -Phase 1 positive results, planning to proceed with phase 2b and phase this year (in PD with and w/o LRRK2 mutations)

Take Home Points

- There are a variety of different formulations of carbidopa/levodopa. Discuss with your doctor which is best for you.
- Protein from the diet can interfere with levodopa absorption in some people
- There are some important side effects to be aware of when taking dopamine agonists, however, they can be an effective treatment for many people with PD.
- There are many strategies to reduce dyskinesia and/or OFF time
- Numerous clinical trials for PD treatments are underway

Resources for more information

- Parkinson's Foundation→PD Library→Medications
  - https://www.parkinson.org/pd-library/books/medications
- Michael J Fox Foundation→Medications and Treatments
  - https://www.michaeljfox.org/medications-treatments
- UpToDate→Patient education Parkinson's Disease Treatment Options—Medications
  - https://www.uptodate.com/contents/parkinson-disease-treatment-options-medications-beyond-the-basics