# Medication Management for Parkinson Disease

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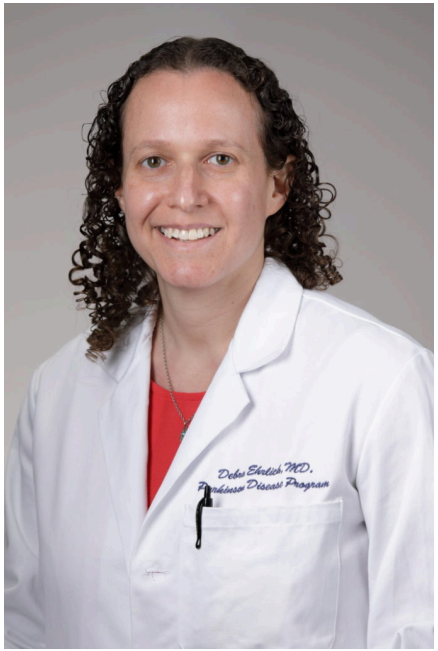


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# Disclosures

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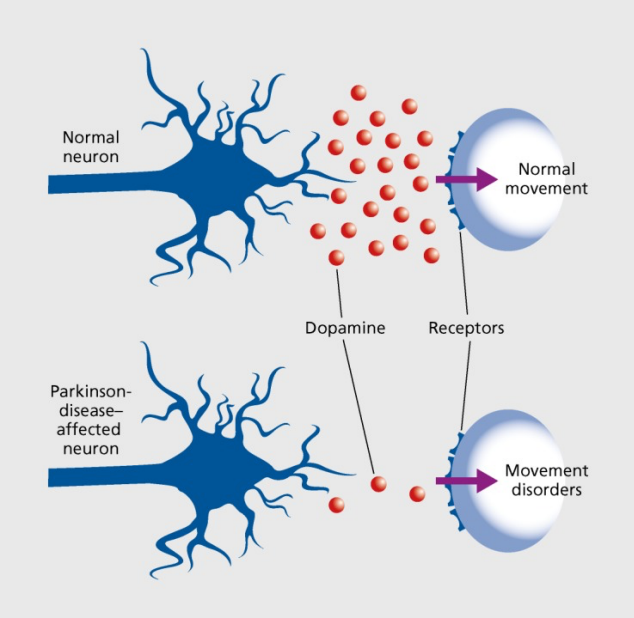
# Overview

- Role of dopamine in Parkinson’s Disease
- Medications for treatment of Parkinson’s Disease
- Important treatment considerations

# The role of dopamine in PD

- Dopamine
  - Neurotransmitter or chemical messenger in the brain
  - Dopamine sends signals in the brain to coordinate movement and other important functions
  - In Parkinson's Disease, brain cells (neurons) that make dopamine stop working or die
  - Lack of dopamine in the brain causes problems with movement and other functions
  - Many of the medications used to treat PD work to increase the function of dopamine in the brain
- Other
  - Dopamine system is not the only brain system affected in PD
  - Disease process affects other brain networks too

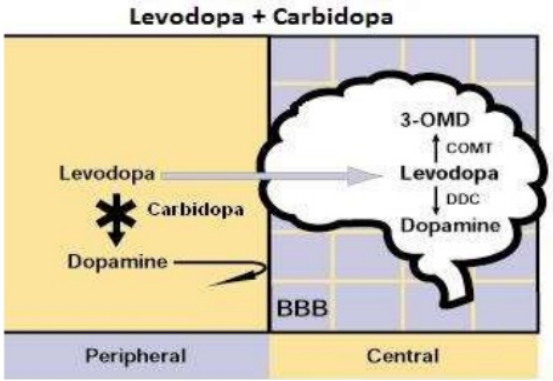


# Levodopa

- Used to treat symptoms of Parkinson’s Disease since the late 1960s
- The chemical structure of dopamine makes it unable to cross the protective blood-brain-barrier, however, levodopa is able to freely enter the brain
- When taken in pill form, it is absorbed by the small intestine to the bloodstream
- It travels through the bloodstream and gets transported to the brain
- Once in the brain, levodopa is absorbed by nerve cells which convert it to dopamine

# The importance of carbidopa

- If 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
- Carbidopa reduces the possible side effect of nausea and allows more levodopa to get to the nerve cells of the brain
- In Canada and Europe, levodopa is combined with benserazide



# Different forms of levodopa

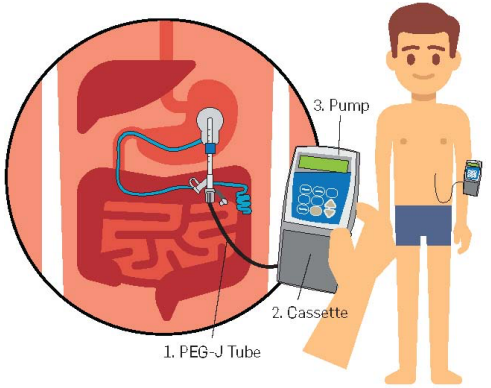
| Generic name | Trade/Brand Name | Important information |
|---|---|---|
| Carbidopa/levodopa immediate release (IR) | Sinemet | Available in 3 doses 10/100, 25/100, 25/250 |
| Carbidopa/levodopa dissolvable | Parcopa | Tablet that dissolves on the tongue |
| Carbidopa/levodopa extended/controlled release (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) |

# Carbidopa/levodopa: Benefits, side effects, and other concerns

- Benefits of levodopa
  - Significant improvement in motor symptoms, usually most effective of all PD medications
  - Few medication interactions
- Common side effects/complications
  - Nausea/vomiting-most common when first starting, take with snack (crackers, toast)
  - Drowsiness
  - Lightheadedness, lower blood pressure
  - Hallucinations or confusion
- Other concerns
  - Motor complications may develop with long-term use
    - Dyskinesia
    - OFF time
  - Protein effect
    - Dietary protein and levodopa absorbed in same place in small intestine, high protein meal could decrease amount of levodopa absorbed and reduce effect of that dose

# Carbidopa/levodopa intestinal gel (Duopa)

- Gel form of carbidopa/levodopa
- Administered through a tube directly to the small intestine
- Tube placed surgically, then an external pump is used to administer the medication
- Approved for use in advanced Parkinson's Disease
  - Motor fluctuations with 3+ hours of OFF time
  - Tried and failed to control motor fluctuations with another class of medications
- Can be given continuously for up to 16hrs/day, extra doses can be administered
- May reduce OFF time and dyskinesia
- Side effects: device-related complications



# Inhaled levodopa (Inbrija)

- FDA approved December 2018
- Inhaled, dry powder formulation of levodopa
- Bypasses metabolism in the GI tract/liver by going directly from lungs to bloodstream
- Rescue therapy to treat OFF periods
- Used as an add-on treatment only
- Quick onset of action
  - Onset of effect 10 minutes
  - Peak effect 30 minutes
- Single dose=2 capsules (each capsule is 42mg)
- Most common side effects: cough, upper respiratory tract infection, sputum discoloration, dyskinesia

# Dopamine Agonists

- Group of medications that mimic the effects of dopamine
- 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 |

# Dopamine agonists: Pros and cons

| Pros | Cons |
| --- | --- |
| Improve motor symptoms of PD | Less effective than levodopa |
| Effects last longer than levodopa | Similar side effects to levodopa (higher risk for low blood pressure) |
| May be less likely to lead to dyskinesia or OFF fluctuation | Sleep attacks: sudden unanticipated onset of sleep |
| Can be used alone or in combination with other treatments | Impulse control disorders: compulsive gambling, excessive shopping, hypersexuality, compulsive eating |
| Do not compete with protein for absorption, no dietary restrictions | Repetitive, somewhat purposeless activities like organizing, sorting, or collecting items |

# MAO-B Inhibitors

- Slows down the breakdown of dopamine in the brain by blocking an enzyme (monoamine oxidase type B), which breaks down dopamine after it does its work
- This allows dopamine to function for a longer period of time
- Results in modest benefit in PD motor symptoms
- Can be used as monotherapy in early stages of PD or can be used as add-on therapy
- When used with other PD medications, may extend ON time and reduce OFF time

# Available MAO-B Inhibitors

| Generic name | Trade name | Important information |
|---|---|---|
| Rasagiline | Azilect | Dosed 1x per day |
| Selegiline | Eldepryl (pill)<br>Zelapar (tablet dissolves in mouth) | Dosed 2x per day, metabolized to a stimulant which can cause jitteriness, insomnia, confusion |
| Safinamide | Xadago | Approved only as an add-on therapy to reduce OFF time only, may cause dyskinesia |

# MAO-B Inhibitors: Side effects and cautions

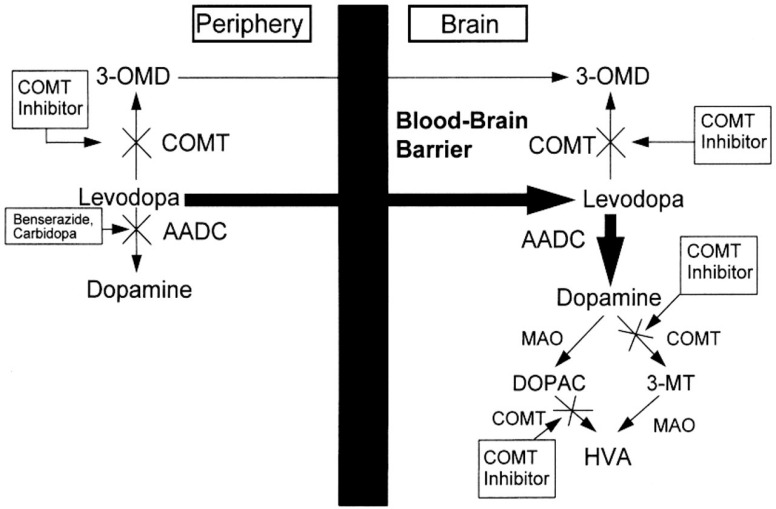
- Common side effects:
  - Mild nausea, dry mouth, constipation, lightheadedness
- Rare, severe drug interaction: Serotonin syndrome
  - This is a potential interaction that can occur if taken with antidepressants or other medications that increase levels of serotonin
  - Could be life-threatening
  - Make sure that your doctors are aware of all other medications you are taking
- Dietary concerns?
  - When taken in high doses and combined with large amounts of food that contain tyramine (aged cheeses, cured meats, etc.) MAO-B inhibitors can cause increased blood pressure (hypertensive crisis)
  - Typical doses of MAO-B inhibitors used in PD are low and usually do not cause this side effect, though you may see this warning on your pill bottle

# Are MAO-B Inhibitors Neuroprotective?

- Animal studies showed that MAO-B inhibitors might slow the progression of PD
- A clinical trial in the 1980s showed a 9-month delay in need to begin levodopa in group who took selegiline vs placebo
  - While many interpreted these results as suggestions that selegiline had neuroprotective effects, the benefit may simply have been the result of improvement in motor symptoms from the selegiline
- More recent studies of MAO-B inhibitors have not supported neuroprotective effects
- The neuroprotective possibilities of MAO-B inhibitors remains a topic of debate among experts

# COMT Inhibitors

- Catechol-o-methyltransferase (COMT) is an enzyme that deactivates levodopa
- COMT inhibitors help slow the breakdown of levodopa, making more available to the brain
- This can increase the duration of benefit for each levodopa dose
- Increase ON time, reduce OFF time, reduce end of dose wearing off



# Available COMT Inhibitors

| Generic name | Trade name | Important information |
|---|---|---|
| Entacapone | Comtan | Must be given at the same time as carbidopa/levodopa dose |
| Tolcapone | Tasmar | Three times daily dosing, risk of liver toxicity, requires blood monitoring of liver function |
| Opicapone | Ongentys | Taken once daily at bedtime |
| Carbidopa/levodopa/entacapone | Stalevo | Combines carbidopa/levodopa + entacapone into one pill |

# COMT Inhibitors: Special considerations and side effects

- Important features
  - COMT inhibitors work by increasing benefits of levodopa, reduce OFF time, increase ON time
  - No benefit on PD symptoms if not taken with levodopa
  - If OFF time is a problem, COMT inhibitors may be used instead of increasing levodopa dose
- Common side effects
  - Discoloration of urine (orange, reddish brown, rust colored)-this is harmless
  - Diarrhea
  - Similar side effects to levodopa, such as worsening  of dyskinesia
  - Risk of liver damage with tolcapone only

# Amantadine

- Amantadine is an antiviral drug initially developed to treat influenza
- In the late 1960s, it was noticed that people with PD who took amantadine experienced improvement in tremor and other PD symptoms
- Exact mechanism of action in the brain is not known
- Can be used alone to treat mild PD motor symptoms or taken with other PD medications
- Can reduce dyskinesia and OFF time (only Gocavri FDA approved for this purpose, others off label)

# Available formulations of amantadine

| Generic Name | Trade Name | Important information |
|---|---|---|
| Amantadine | Symmetrel | Usually taken 2-3 times per day |
| Amantadine extended-release capsules | Gocavri | Taken once daily at bedtime, FDA approved to treat dyskinesia and OFF time |
| Amantadine extended-release tablets | Osmolex ER | Taken once daily in the morning |

# Amantadine: Common side effects

- Insomnia (amantadine IR and Osmolex only)
  - Can be avoided if not taken close to bedtime
  - May improve daytime sedation
- Dry mouth, dry eyes
- Nausea
- Dizziness
- Purplish blotchy rash on skin
- Leg swelling
- Hallucinations
- Dose may need to be reduced in people with kidney problems

# Anticholinergic medications

- There is a balance between dopamine and acetylcholine in the brain
- Reduced levels of dopamine in PD disrupt the balance between dopamine and acetylcholine
- Anticholinergic medications block the effects of acetylcholine in the brain, which can help restore the balance between dopamine and acetylcholine

# Available anticholinergics

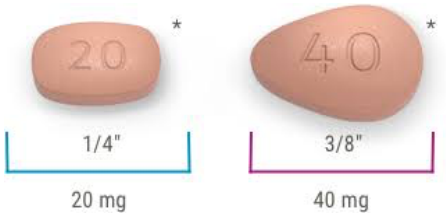
| Generic name | Trade Name | Important Information |
|---|---|---|
| Trihexyphenidyl | Artane | Dosing usually 2-3x per day |
| Benztropine | Cogentin | Dosing usually 2-3x per day |

# Pros and cons of anticholinergics

- Pros
  - Can be useful in treating tremor and dystonia
- Cons
  - Usually better tolerated in younger people, side effects more likely in older individuals
  - Use with caution in people with glaucoma
  - Common side effects
    - Dry mouth (could be helpful for drooling)
    - Dry eyes
    - Blurry vision
    - Urinary retention
    - Constipation
    - Cognitive slowing, short term memory loss, confusion

# Adenosine receptor antagonist

- Blocks brain chemical called adenosine
- Blockade of adenosine helps to increase dopamine signaling in the brain
- Istradefylline (Nourianz)
  - FDA approved in August 2019 as an add on agent to carbidopa/levodopa to treat OFF time
  - Taken once daily
  - Common side effects:
    - Nausea, constipation, insomnia, dyskinesia, hallucinations
    - May cause modest increase in dyskinesia



# Important treatment considerations

- Individualized therapy
  - There is no standard treatment for PD
  - Each person with PD has a unique set of symptoms, response to medications, and other important factors to consider
- Overall goals of treatment
  - Use the lowest doses of medication needed to maximize benefit and minimize side effects
- Your medications and dosing will likely change over time

# When should medications for PD be started?

- Varies from person to person
- When symptoms interfere with work or daily activities
- Balance is impaired
- When symptoms cause increased risks

# Medication needs will change over time

- Early PD/Mild symptoms
  - Will usually start with a single medication, low dose
  - With the right dose, benefits usually smooth throughout the day
  - Effects of late or missed dose may not be noticed
- Moderate-Advanced PD
  - May start to notice PD symptoms breaking through before time to take next dose (wearing OFF)
  - Doses may be increased and/or additional medications added to reduce OFF time
  - With increasing doses of medications, more likely to develop side effects such as dyskinesia
  - Additional medications may be added to treat side effects
  - Surgical therapies may be considered

# Summary

- Many different medications available to treat the motor symptoms of Parkinson's Disease
- Dopamine is reduced in Parkinson's disease
- Many of the available medications work to increase the amount or action of dopamine in the brain
- There is no standard treatment regimen for PD
- Your PD doctor will work with you to develop an individualized treatment plan
- Your medications and doses will change over time
- Overall goal of treatment: maximize benefits while minimizing side effects

# 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