Medication Management for Parkinson Disease
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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

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

www.Parkinson.org
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

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<tr>
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<tbody>
<tr>
<td>Pramipexole</td>
<td>Mirapex</td>
<td>Usually dosed 3x per day</td>
</tr>
<tr>
<td>Pramipexole ER</td>
<td>Mirapex ER</td>
<td>Usually dosed 1-2x per day</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Requip</td>
<td>Usually dosed 3x per day</td>
</tr>
<tr>
<td>Ropinirole extended release (XL)</td>
<td>Requip XL</td>
<td>Usually dosed 1-2x per day</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>Neupro</td>
<td>Transdermal patch, delivers medication through the skin directly to bloodstream, bypasses stomach</td>
</tr>
<tr>
<td>Apomorphine subcutaneous</td>
<td>Apokyn</td>
<td>Injected under skin, quick onset of action, used as rescue for OFF time, must be started with anti-nausea medication</td>
</tr>
<tr>
<td>Apomorphine sublingual</td>
<td>Kynmobi</td>
<td>Sublingual film, dissolves when placed under the tongue, used to treat OFF time</td>
</tr>
</tbody>
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# Dopamine agonists: Pros and cons

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

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

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<tr>
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<th>Important information</th>
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<tbody>
<tr>
<td>Entacapone</td>
<td>Comtan</td>
<td>Must be given at the same time as carbidopa/levodopa dose</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Tasmar</td>
<td>Three times daily dosing, risk of liver toxicity, requires blood monitoring of liver function</td>
</tr>
<tr>
<td>Opicapone</td>
<td>Ongentys</td>
<td>Taken once daily at bedtime</td>
</tr>
<tr>
<td>Carbidopa/levodopa/entacapone</td>
<td>Stalevo</td>
<td>Combines carbidopa/levodopa + entacapone into one pill</td>
</tr>
</tbody>
</table>
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

<table>
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<tr>
<th>Generic Name</th>
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<th>Important information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>Symmetrel</td>
<td>Usually taken 2-3 times per day</td>
</tr>
<tr>
<td>Amantadine extended-release capsules</td>
<td>Gocavri</td>
<td>Taken once daily at bedtime, FDA approved to treat dyskinesia and OFF time</td>
</tr>
<tr>
<td>Amantadine extended-release tablets</td>
<td>Osmolex ER</td>
<td>Taken once daily in the morning</td>
</tr>
</tbody>
</table>
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

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<tr>
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<th>Important Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trihexyphenidyl</td>
<td>Artane</td>
<td>Dosing usually 2-3x per day</td>
</tr>
<tr>
<td>Benztropine</td>
<td>Cogentin</td>
<td>Dosing usually 2-3x per day</td>
</tr>
</tbody>
</table>
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