

# Medications in Parkinson's Disease

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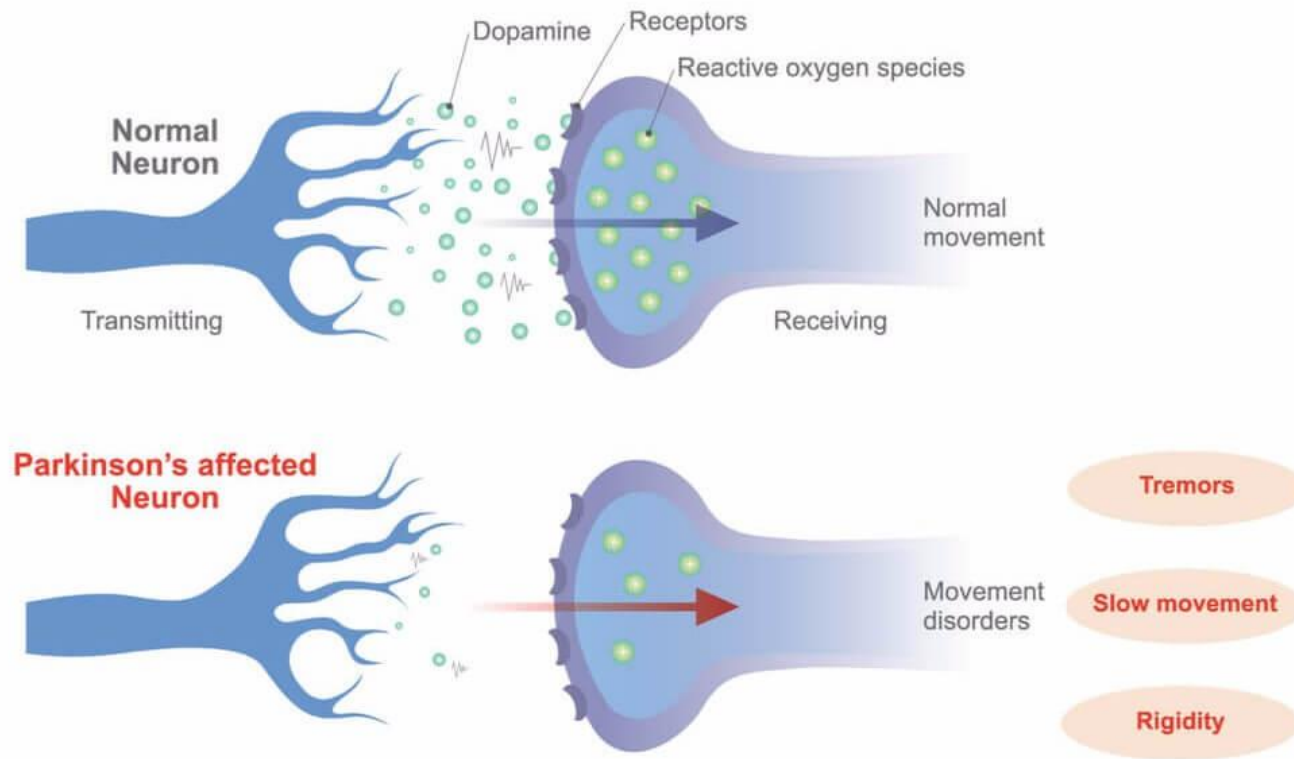
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# Objectives

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- ❖ Discuss pathophysiology in regards to medication dosing in Parkinson's disease
- ❖ Discuss common Parkinson's medications and how to optimize "on" periods
- ❖ Review medications for non-motor symptoms

# Parkinson's pathophysiology



# Symptoms

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## Motor

- Tremor
- Rigidity
- Bradykinesia (slowness of movements)
- Postural instability: trouble with balance and falls

## Non-motor

- Constipation
- Bladder changes
- Mood disturbances
- Sleep disturbances
- Cognitive changes
- Low blood pressure
- Pain

# Medication therapy

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- ❖ Medication regimens can be complex and can truly be a balancing act
- ❖ Patients may need frequent dosing of multiple different therapies to control symptoms
- ❖ You may hear providers discuss “on” and “off” times
  - “On” periods are times when the medications are working well and symptoms are less noticeable
  - “Off” periods are times when the medication’s effect has worn off and symptoms return or worsen
- ❖ In general, medications are started at low doses and increased slowly to reduce adverse effects

# Motor symptoms

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FOCUS ON THERAPY



# Carbidopa/levodopa

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- ❖ Main Parkinson's therapy
- ❖ Levodopa is the immediate precursor to dopamine
  - Able to cross the blood brain barrier and bind to dopamine receptors
  - Allows the depleted number of dopaminergic neurons to produce dopamine and alleviate symptoms
- ❖ Carbidopa blocks the metabolism of levodopa in the periphery
- ❖ Most potent medication but has a short half life
  - Have to take frequent doses to alleviate symptoms

# Carbidopa/levodopa products

Medication (brand)	Dosages	Typical dose	Side effects	Use in Parkinson's
Carbidopa/levodopa immediate release tablets (Sinemet)	10/100 mg 25/100 mg 25/250 mg	150-2,000 mg of levodopa daily in divided doses	Low blood pressure, dizziness, nausea, constipation, behavior changes, <b>involuntary movements of the face, arms or legs</b>	To help manage symptoms of PD (slowness, stiffness, tremor, etc.)
Carbidopa/levodopa immediate release tablets (Dhivy)	25/100 mg	Up to 8 tablets per day		May be good agent for people with difficulty cutting tablets
Carbidopa/levodopa immediate release orally disintegrating tablets (Parcopa)	10/100 mg 25/100 mg 25/250 mg	150-2,000 mg of levodopa daily in divided doses		May be appropriate for people with swallowing difficulties
Carbidopa/levodopa controlled release tablets	25/100 mg 50/200 mg	200-2,400 mg of levodopa daily in divided doses		Same as above
Carbidopa/levodopa extended release capsules (Rytary)	23.75/95 mg 36.25/145 mg 48.75/195 mg 61.25/245 mg	855-2,340 mg of levodopa daily in divided doses		Same as above



# Carbidopa/levodopa products cont.

Medication (brand)	Dosages	Typical dose	Side effects	Use in Parkinson's
Carbidopa/levodopa/entacapone tablets (Stalevo)	12.5/50/200 mg 18.75/75/200 mg 25/100/200 mg 31.25/125/200 mg 37.5/150/200 mg 50/200/200 mg	150-1,200 mg of levodopa/day	Low blood pressure, dizziness, nausea, constipation, behavior changes, diarrhea, discolored urine	Replacement for immediate-release carbidopa/levodopa to help with "on/off" fluctuations
Carbidopa/levodopa enteral suspension (Duopa) via surgically implanted tube in small intestine	4.86/20 per mL	Up to 2,000 mg of levodopa over 16 daytime hours	Low blood pressure, dizziness, nausea, constipation	For treatment of "on/off" fluctuations in advanced Parkinson's
Levodopa inhalation powder capsules (Inbrija)	42 mg	84 mg inhaled by mouth up to 5 times/day as needed	Same as above, cough, upper respiratory infection	Used with carbidopa/levodopa for sudden "off" episodes

# How to correctly take your carbidopa/levodopa

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- ❖ Set a timer to make sure you take your medication exactly when it is due
- ❖ Separate from protein & high fat meals
  - Taking the medication with a stomach full of protein (meats, cheeses, dairy, PB, protein shakes) can delay the tablet from getting from the stomach to the small intestine where it is absorbed
  - The chemicals that make up proteins and carbidopa/levodopa are absorbed in the bloodstream through a similar process
- ❖ Try to schedule meals 2 hours before or 1 hour after a carbidopa/levodopa dose
- ❖ Make sure to drink plenty of water and eat a fiber rich diet to help manage constipation (more on this later)

# Managing “off” time

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- ❖ As Parkinson’s progresses, people can become more sensitive to levodopa and other medications which can lead to increased side effects
- ❖ Wearing off symptoms vary for each person
  - Slower movements, feeling stiffer, tremor may worsen
  - Non-motor symptoms such as anxiety, depression, brain fog, pain, and fatigue may appear or intensify
- ❖ Track symptoms!
  - Can discuss with doctor when off periods are occurring
  - Pay attention to medication timing in regards to meals as well as other factors like stress, physical activity, constipation

# Managing “off” time cont.

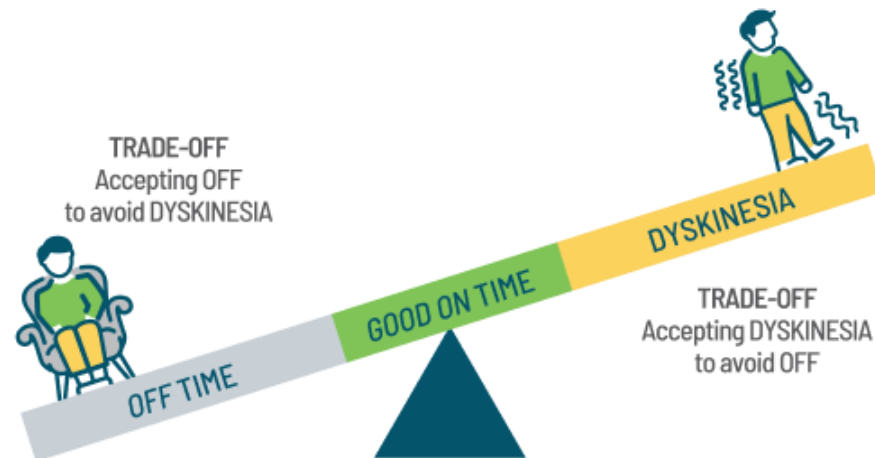
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- ❖ Your doctor may adjust your medication in the following ways:
  - Increase your dose
  - Take your dose more frequently
  - Switch to or add an extended release carbidopa/levodopa product or a dopamine agonist
  - Trial a quick acting levodopa or apomorphine medication for sudden “off” periods
  - Add medications that help boost dopamine (COMT inhibitor or MAO-B inhibitors)
- ❖ Can also explore surgical options, if appropriate

# Managing dyskinesias

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- ❖ Dyskinesias are the abnormal involuntary movements of face, arms and legs that patients may experience as a medication side effect
  - May include rapid jerking or muscle spasms
  - Rhythmic, dance like movements
- ❖ Important to discuss these side effects with physician
  - Dose reduction or adjustment in medication may help reduce this adverse effect



# Dopamine agonists

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- ❖ Work by stimulating dopaminergic receptors in the central nervous system
- ❖ Less potent than carbidopa/levodopa
- ❖ Benefit: less likely to cause dyskinesias and have a longer half-life
- ❖ Pitfall: Increased risk of hallucinations, hypotension, somnolence, leg edema and risk of compulsive behaviors (including sexual behavior, buying, or gambling)
  - Risk of hypotension higher in elderly patients

# Dopamine agonists

Medication (brand)	Dosages	Typical dose	Side effects	Use in Parkinson's
Ropinirole (Requip)	0.25, 0.5, 1, 2, 3, 4, or 5 mg tablets	9-24 mg total/day in 3 separate doses	Dizziness, orthostatic hypotension, leg swelling, nausea, <b>fatigue</b> , <b>drowsiness</b> , confusion, behavioral changes <b>including impulsive behaviors</b>	For Parkinson's movement symptoms and restless leg syndrome
Ropinirole extended release (Requip XL)	4, 6, 8, or 12 mg tablets	8-24 mg once/day		
Pramipexole (Mirapex)	0.125, 0.25, 0.5, 0.75, 1 or 1.5 mg tablets	1.5-4.5 mg total/day in 3 doses		
Pramipexole extended release (Mirapex ER)	0.375, 0.75, 1.5, 2.25, 3, 3.75, or 4.5 mg tablets	1.5-4.5 mg once/day		
Rotigotine (Neupro)	2, 4, 6 or 8 mg patches	4-8 mg once/day	Same as above, plus skin irritation	Same as above
Apomorphine subcutaneous injection (Apokyn)	0.1-0.6 mL	Use as needed up to 5 times per day	Site reaction, orthostatic hypotension, confusion, excessive daytime sleepiness, impulsive behaviors, hallucinations	"Rescue" or on-demand medication for "off" episodes

# COMT & MAO-B inhibitors

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- ❖ Catechol-O-methyl transferase (COMT) and monoamine oxidase aldehyde dehydrogenase B (MAO-B) inhibitors
  - Block enzymes that breakdown dopamine
  - Help prolong the effect of carbidopa/levodopa
- ❖ May also increase the side effects of levodopa
  - Hallucinations
  - Dyskinesias
  - Nausea
- ❖ MAO-B inhibitors have multiple drug interactions including antidepressants



# COMT inhibitor

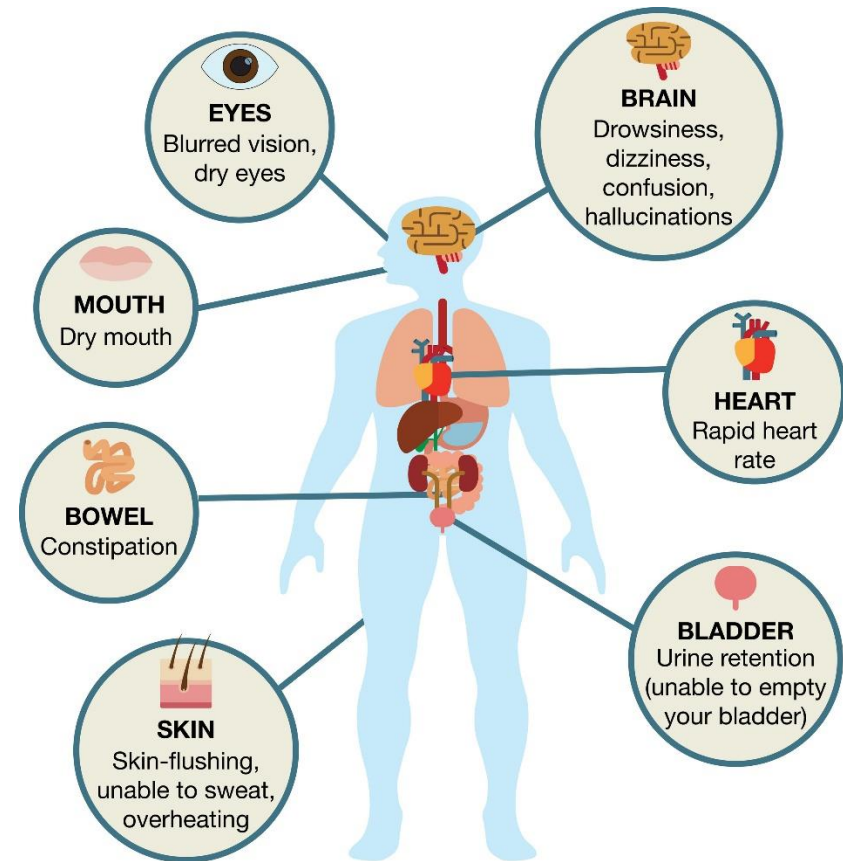
Medication (brand)	Dosages	Typical dose	Side effects	Use in Parkinson's
Entacapone (Comtan)	200 mg tablets	200 mg tablet taken with each dose of carbidopa/levodopa	Confusion, dizziness, low blood pressure, hallucinations, red-brown urine, nausea, diarrhea, may intensify dyskinesia	Increase benefit of levodopa and reduce "off" periods

# MAO-B inhibitors

Medication (brand)	Dosages	Typical dose	Side effects	Use in Parkinson's
Selegiline	5 mg capsules or tablets	5 mg twice/day at breakfast & lunch	Mild nausea, dry mouth, dizziness, constipation, multiple drug interactions	For Parkinson's movement symptoms or to reduce "off" time when added to levodopa
Orally disintegrating tablet (Zelapar)	1.5, 2.5 mg tablets	1.5-2.5 mg once/day		
Rasagaline (Azilect)	0.5, 1 mg tablets	Up to 1 mg once/day		Same as above
Safinamide (Xadago)	50, 100 mg tablets	Up to 100 mg once/day		To increase benefit of levodopa or to decrease "off" time
Zonisamide (Zonegran)	25, 50, 100, 200 mg tablets	25-200 mg daily	Sleepiness, loss of appetite	Used in Japan for "off" times (not commonly used in US)

# Second line alternatives

- ❖ Can be added on to help with Parkinsonian symptoms (i.e. tremor)
- ❖ Amantadine is more commonly used for treatment of dyskinesias
- ❖ Some of these therapies are anti-cholinergic medications (trihexyphenidyl & benztropine) and are contraindicated in patients with dementia and those > 70 years old
  - Anticholinergic effects: dry mouth, constipation, nausea, blurry vision, urinary retention, dizziness, altered mental status



# Second line

Medication (brand)	Dosages	Typical dose	Side effects	Use in Parkinson's
Amantadine  *extended release also available as Osmolex ER or Gocovri	100 mg capsules	200 mg daily	Nausea, insomnia, dry mouth, lightheadedness, confusion, swollen feet, hallucinations	For levodopa-induced dyskinesia and symptoms of Parkinson's
Trihexyphenidyl (Artane)	2 or 5 mg tablets  2 mg/5 mL elixir	1-2 mg 2-3 times/day	Confusion, drowsiness, forgetfulness, hallucinations, lightheadedness, dry mouth, increased heart rate, urinary retention, falls	For tremor and dystonia, especially in early-onset PD, should be avoided in older adults
Benzotropine (Cogentin)	0.5 mg capsule  1 or 2 mg tablet	Up to 6 tablets taken at bedtime or divided into 2-3 doses/day	Same as above	Same as above

# Non-motor symptoms

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FOCUS ON THERAPY



# Constipation

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- ❖ Can be caused by disease itself or medications used to treat it
- ❖ Can impact absorption of medications if goes untreated
- ❖ Therapies available to try:
  - Polyethylene glycol (Miralax) – available over the counter (OTC)
  - Senna – available OTC
  - Docusate - available OTC
  - Milk of magnesia - available OTC
  - Magnesium citrate - available OTC
  - Lubiprostone (Amitiza) - prescription
  - Linaclotide (Linzess) – prescription
  - Lactulose – prescription

# Orthostatic hypotension (low BP)

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- ❖ Can cause dizziness, lightheadedness, syncope or passing out
- ❖ Prescription therapies available to try:
  - Droxidopa (Northera)
  - Fludrocortisone
  - Midodrine
- ❖ If taking any of the above medications, try to avoid laying flat during the day due to the risk of elevated BP
  - The last dose of medication should be taken 3-4 hours before bedtime

# Bladder issues

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- ❖ Dysautonomia can lead to urinary frequency, urgency or incontinence
- ❖ Timing bathroom breaks can be helpful!
- ❖ Prescription therapies available to try:
  - Tamsulosin
  - Terazosin
  - Oxybutynin
  - Solifenacin
  - Tolterodine
  - Mirabegron



# Sleep disturbances

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There are a multitude of reasons why a patient may experience sleep disturbances

- Sleep wake cycle disrupted
- Rigidity and dystonia may lead to trouble turning in bed and discomfort
- Increased urinary frequency at night

Therapies available to try:

- Melatonin - OTC
- Mirtazapine - prescription
- Trazodone - prescription
- Clonazepam - prescription



# Pain

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- ❖ More than 80% of people with PD report experiencing pain
- ❖ Many different types of pain:
  - Dystonic pain: painful muscle spasm (could be curling of foot, toes or hands)
  - Musculoskeletal pain: pain in the muscles, bones, or skeleton
    - Related to rigidity, decreased movement, or arthritis
    - Muscles may feel stiff & achy and joint pain in one shoulder is common
  - Neuropathic pain: occurs when a nerve is crushed or inflamed
    - May feel sharp, electric, tingling, or numb
  - Central pain: difficult to describe but affects ~10% of PD patients
    - Vague symptoms: abdominal pain, reflux, shortness of breath, feeling flushed, pain around mouth, genital or rectal areas, or simply “pain all over”

# How to treat pain

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- ❖ Pain management really needs to be a team based approach with your PD doctor, physical therapist, occupational therapist, and other specialists
- ❖ Tactics to try:
  - Optimize PD medications
  - Exercise & physical therapy
  - Medications to target specific sources of pain
    - Dystonia: muscle relaxants, deep brain stimulation, Botox injection
    - Neuropathic pain: gabapentin, pregabalin, amitriptyline, nortriptyline, lidocaine patches, duloxetine
    - Musculoskeletal pain: ibuprofen, acetaminophen
  - Make sure to treat underlying depression and other health conditions (such as osteoporosis and diabetes) that may contribute to pain
  - Utilize massage and hot/cold therapy as appropriate

# Mood disturbances

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- ❖ Anxiety and depression affect roughly 50% of patients during some point in their disease
- ❖ Treatment: medications and psychological counseling, especially cognitive behavioral therapy
- ❖ Patients may also experience apathy, or loss of motivation
- ❖ Typically selective serotonin reuptake inhibitors (SSRIs) are recommended
  - Citalopram, escitalopram, fluoxetine, sertraline
  - Serotonin & norepinephrine reuptake inhibitors (SNRIs) can also be used
    - Duloxetine, venlafaxine, desvenlafaxine (Pristiq)
- ❖ Other therapies may be added at providers' discretion depending on symptoms and past medical history

Any questions?

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