



2021 Symposium: Empowerment Day for Parkinson's

Medical Management of Motor Symptoms

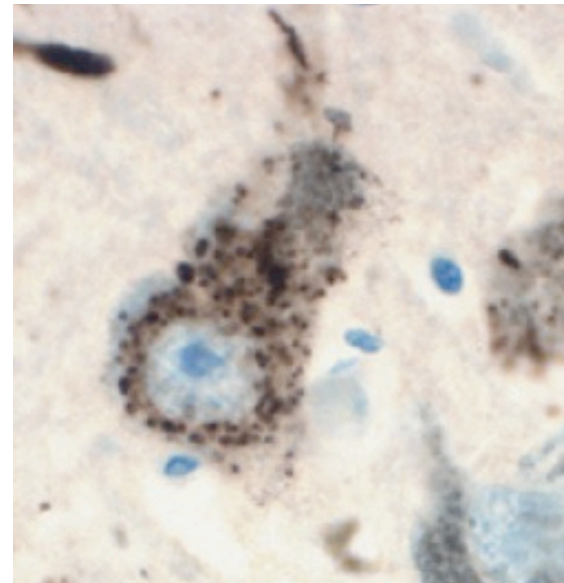
Brenton A. Wright, MD
Assistant Professor of Clinical Neurosciences
December 1, 2021

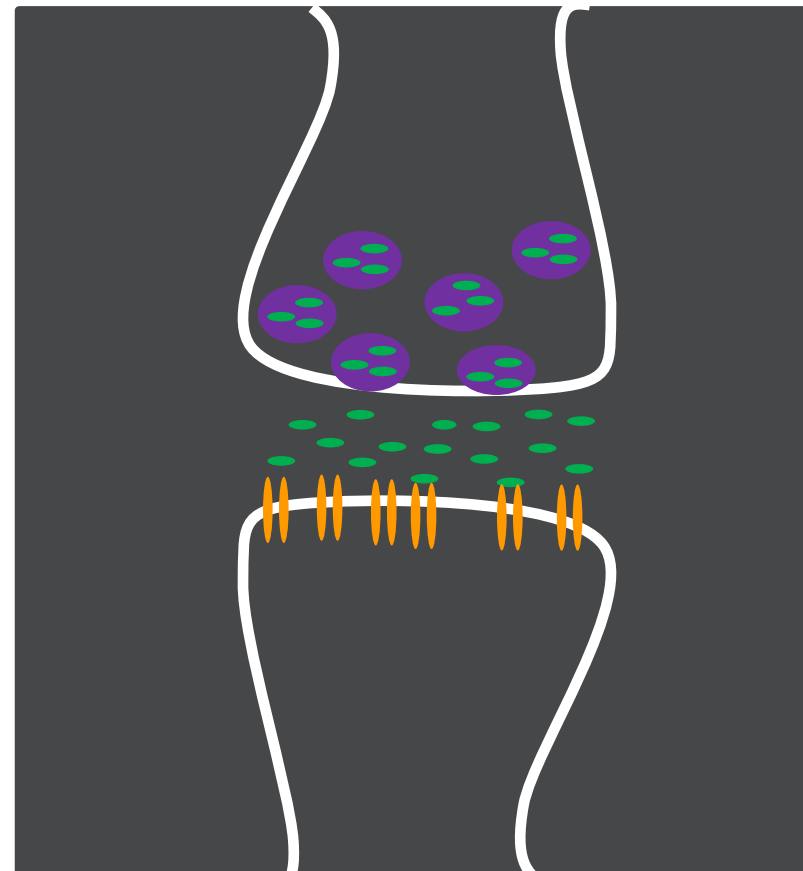
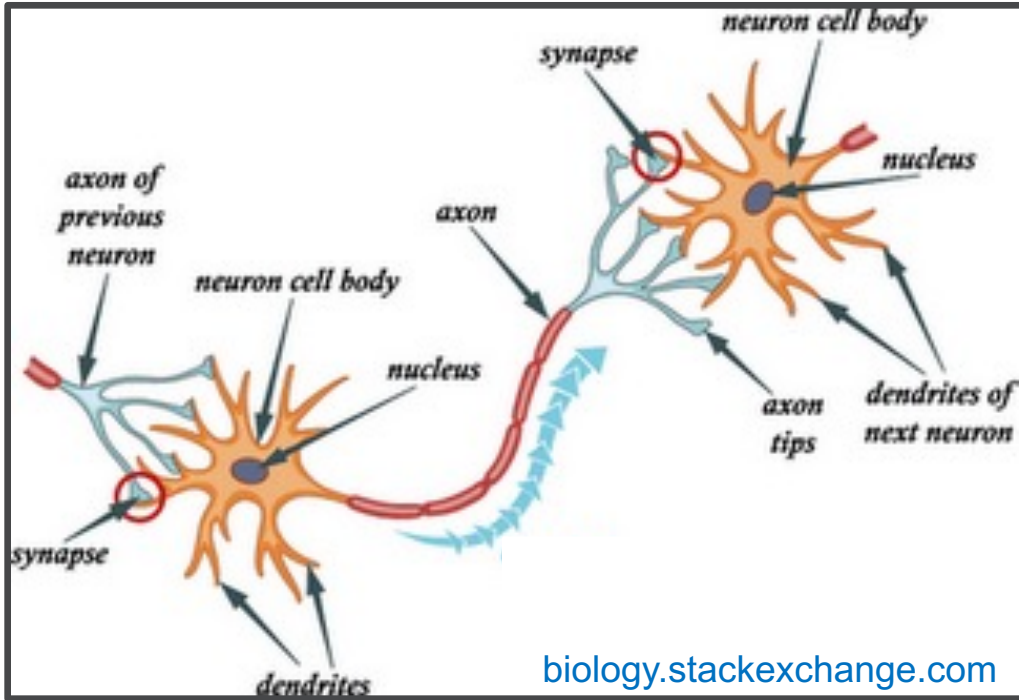
Disclosures –

**Dr. Wright participates in research sponsored by
Acadia, Biogen, Global Kinetics, Neurocrine, Roche, Vaccinex,
Prilenia, and Triplet Therapeutics**

**The UCSD Movement Disorders Fellowship Program receives
grant funding from Abbott, Abbvie, Acadia, Merz, and Medtronic**



The primary pathologic event in Parkinson disease is loss of the dopamine neurons in the substantia nigra (SN_c), which send projections to the medium spiny neurons in the striatum





Dopamine Replacement Therapy:

carbidopa levodopa

- 25/100 mg  25/250 mg
- 10/100 mg 
 - Standard oral formulation (aka Sinemet®)
 - Oral dissolving tablets (aka Parcopa®)
- Usually taken a minimum of three times daily
- Possible side effects:
 - Nausea, abdominal discomfort, dyskinesias, dystonia, worsening of orthostatic hypotension, drowsiness, confusion, hallucinations, paranoia, rash

Carbidopa levodopa: What about the protein effect?

- Some patients with PD find that their levodopa works less effectively when they take it with food (especially protein) or on a full stomach
- However, only ~1/3 of PD patients have this!
- Don't arrange your life/meal schedule around dose times until you do some trial and error and find out if you are one of these patients
- Some patients become nauseated when taking their carbidopa levodopa on an empty stomach, but most do not have this problem

Remember, every person is different!

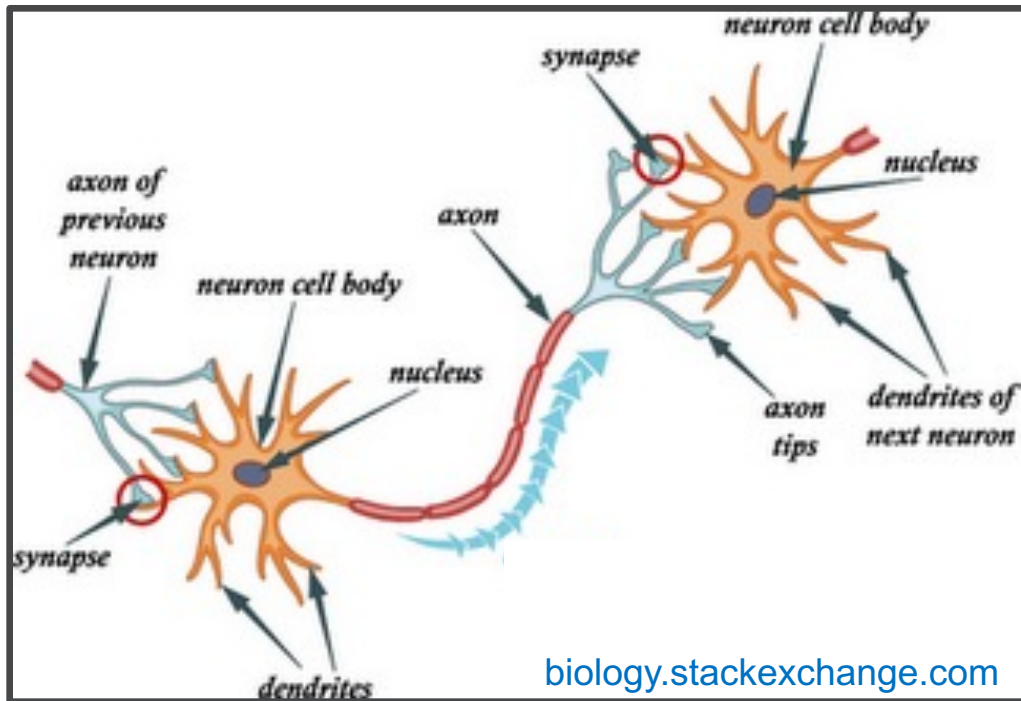
Dopamine Replacement Therapy: dopamine agonists

- **Pramipexole** (aka Mirapex®)
 - 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg
ER: 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, 4.5 mg
- **Ropinirole** (aka Requip®)
 - 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg
ER: 2 mg, 4 mg, 6 mg, 8 mg, 12 mg
- **Rotigotine** (aka Neupro®) patch
 - 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg patches

Possible side effects:

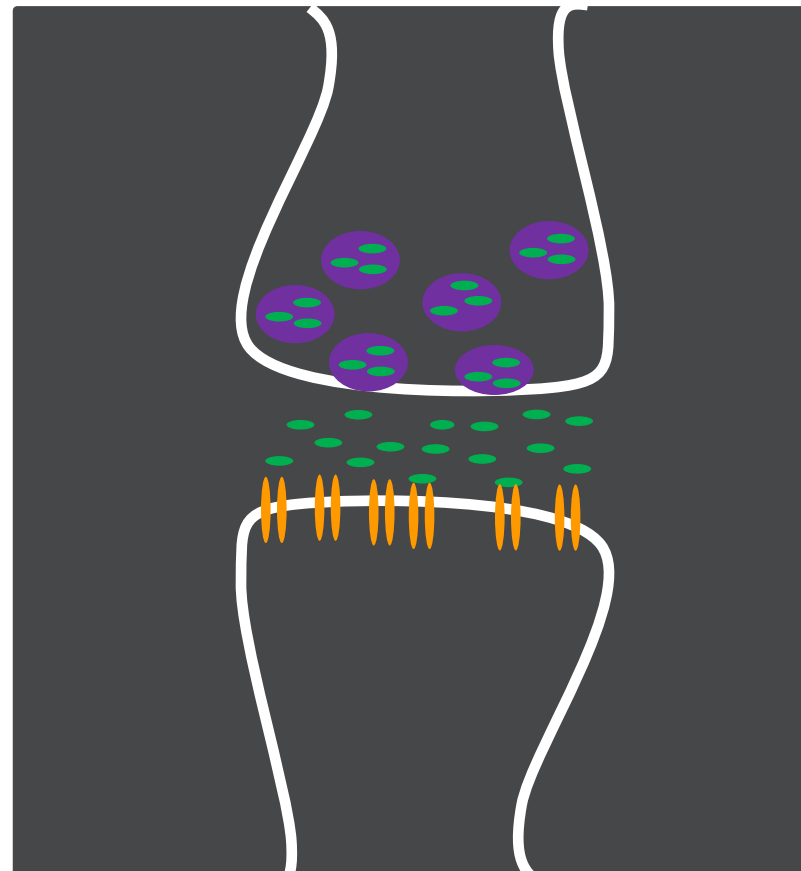
- Worsening of orthostatic hypotension, drowsiness, confusion, hallucinations, impulse control disorders, ankle swelling, paranoia, nausea, abdominal discomfort, dyskinesias, dystonia, rash, withdrawal syndrome

Why do PD patients develop “wearing off?”



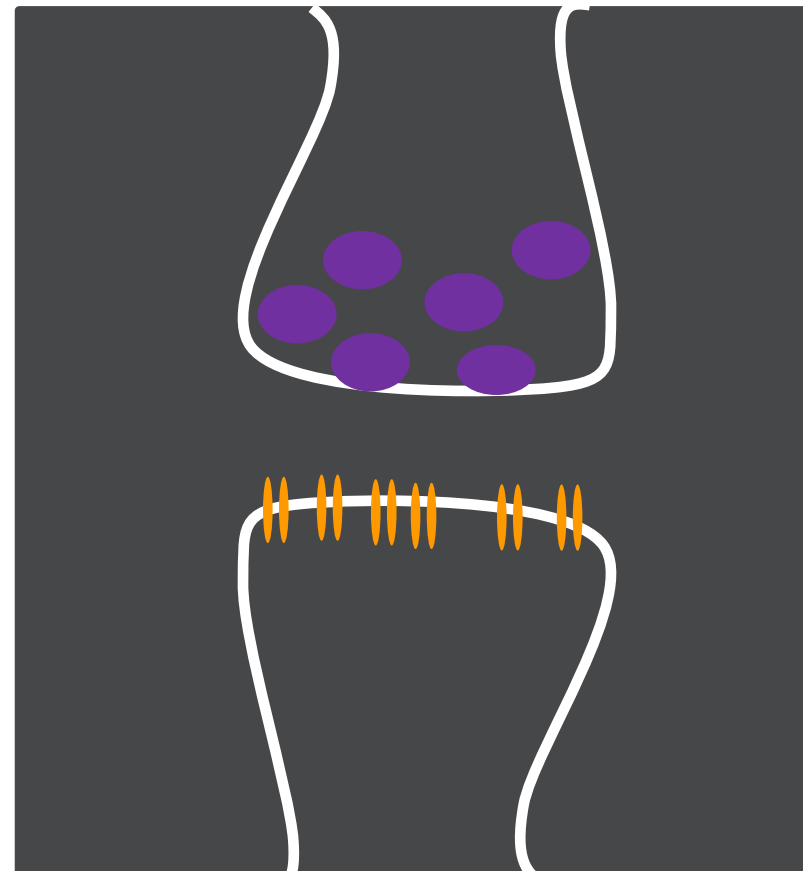
Dopamine neurons:

3-6 Hz tonic firing as well as phasic firing
in response to stimuli



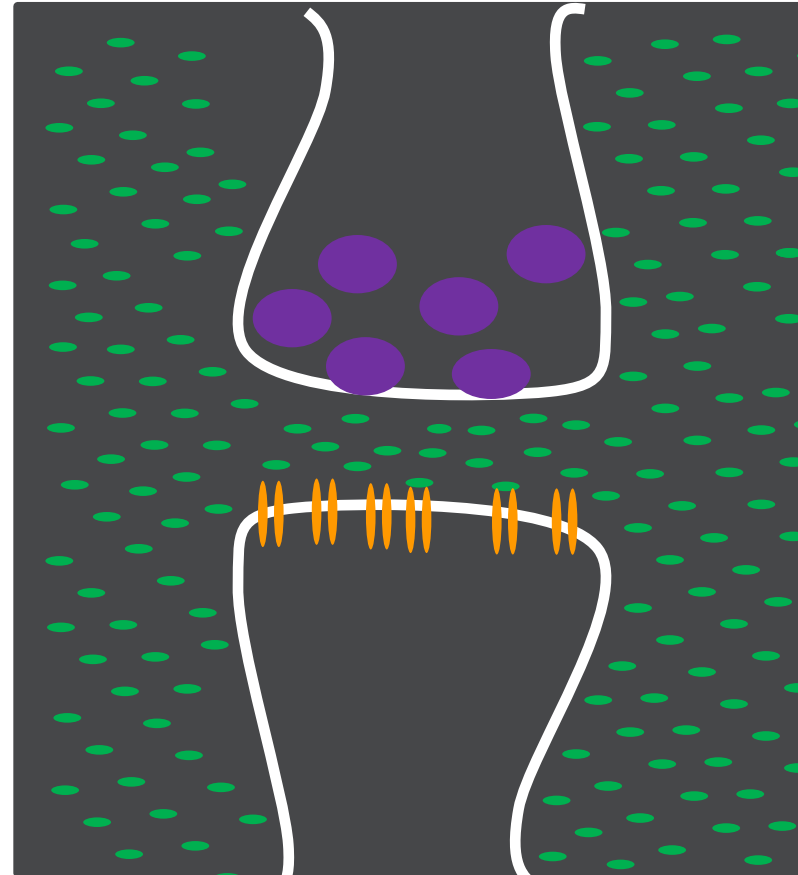
Early PD

- Remaining dopamine neurons are able to take up excess levodopa from the blood and store it as dopamine in the presynaptic terminals



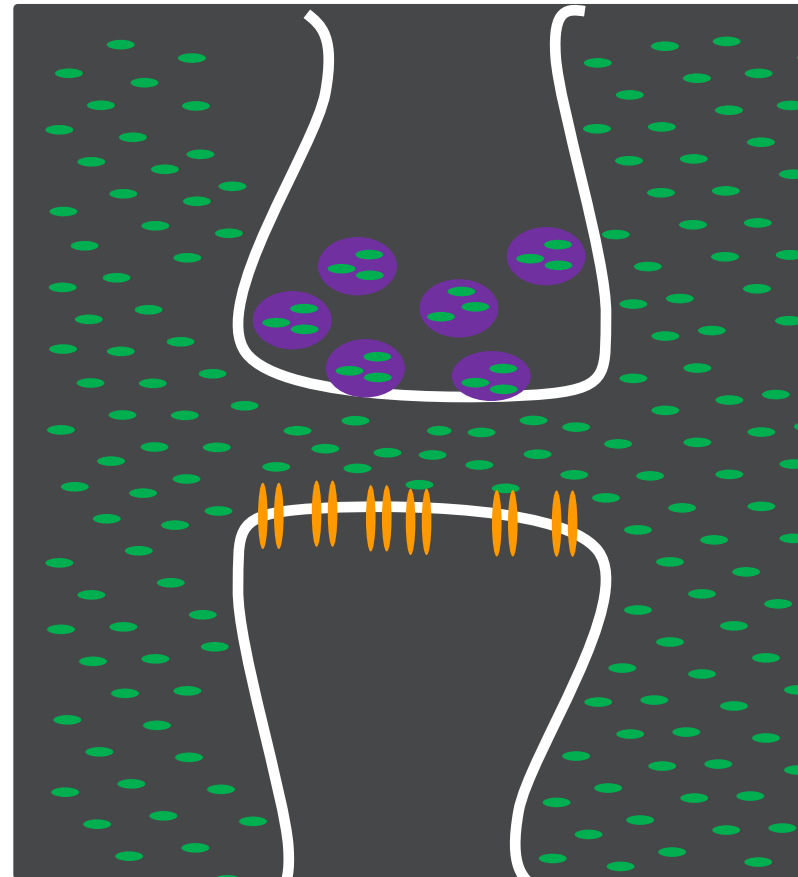
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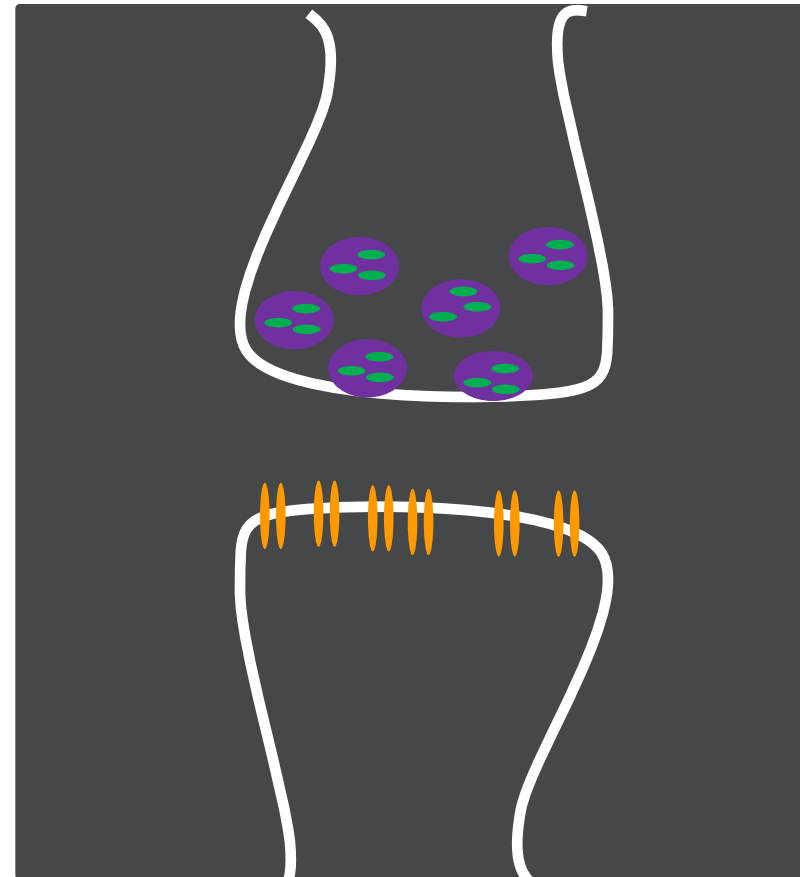
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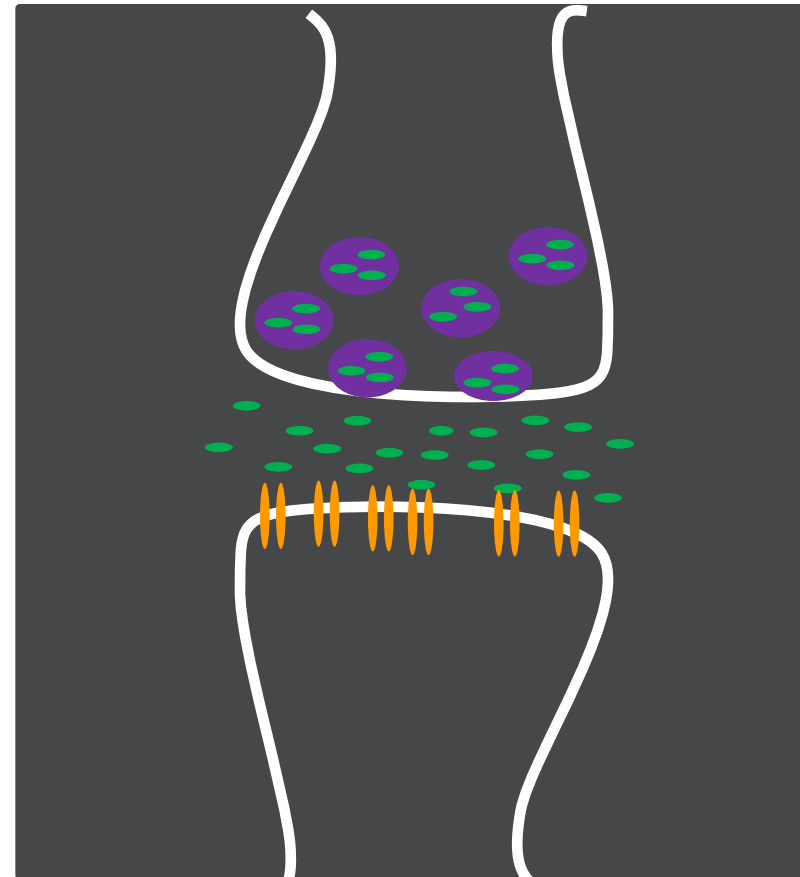
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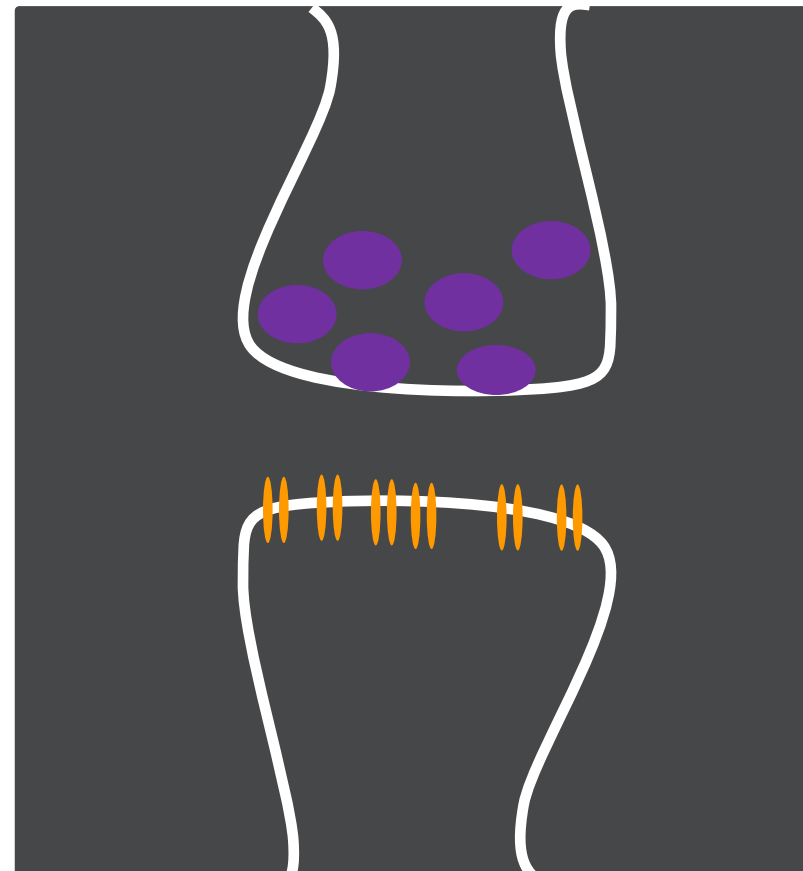
Early PD

- Dopamine concentration maintained at constant levels in part due to presynaptic storage of dopamine



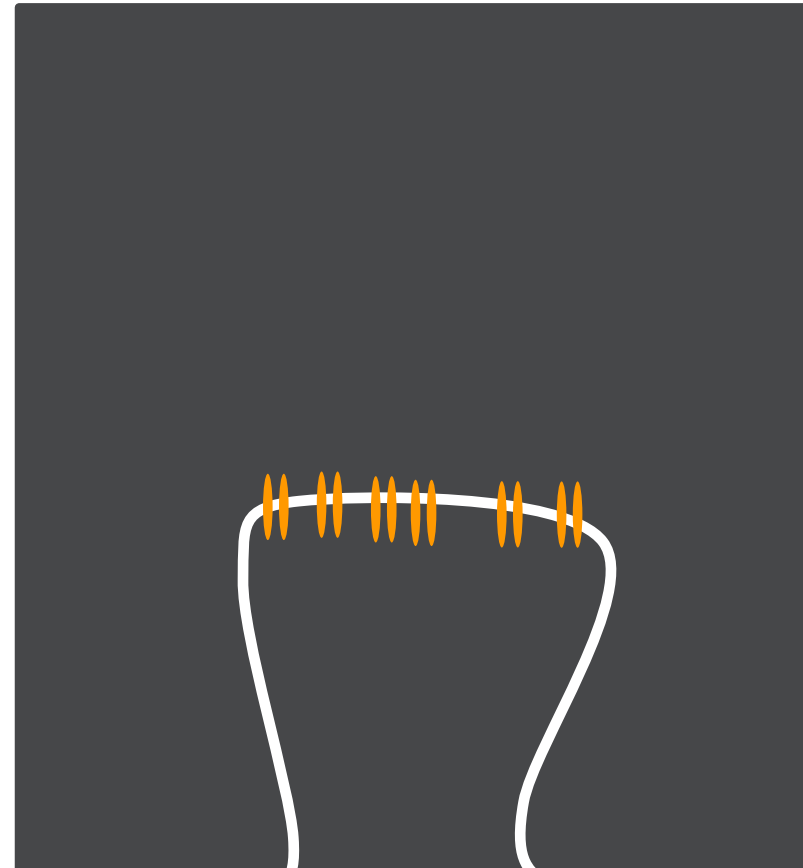
Later PD

- As more dopamine neurons are lost, the presynaptic stores of dopamine become depleted



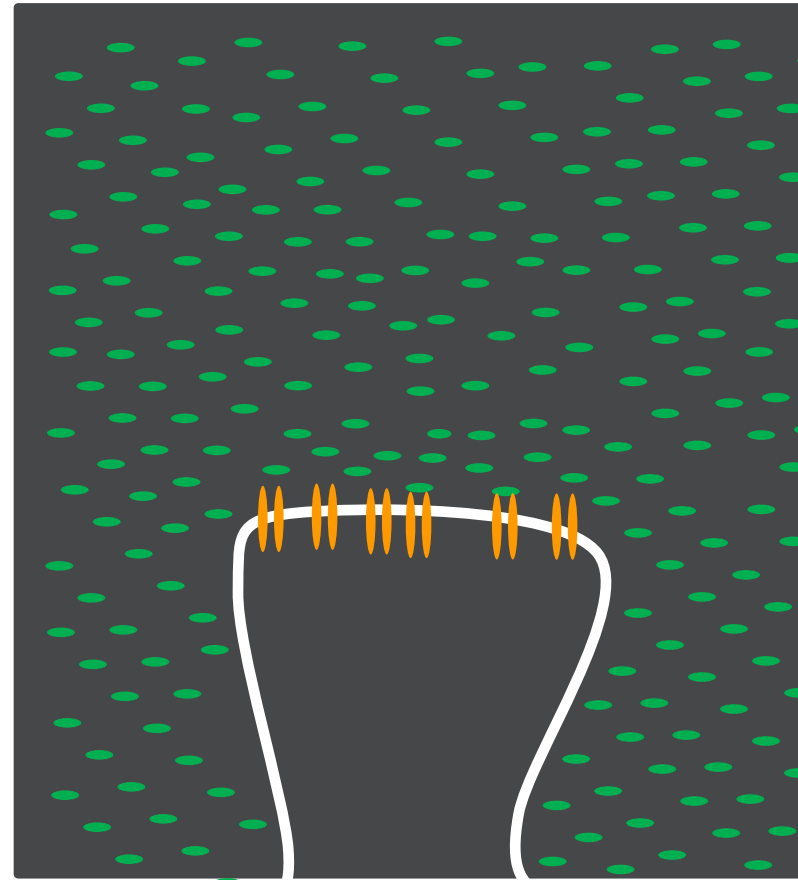
Later PD

- Postsynaptic concentration of dopamine in the striatum becomes closely linked to blood levels of levodopa



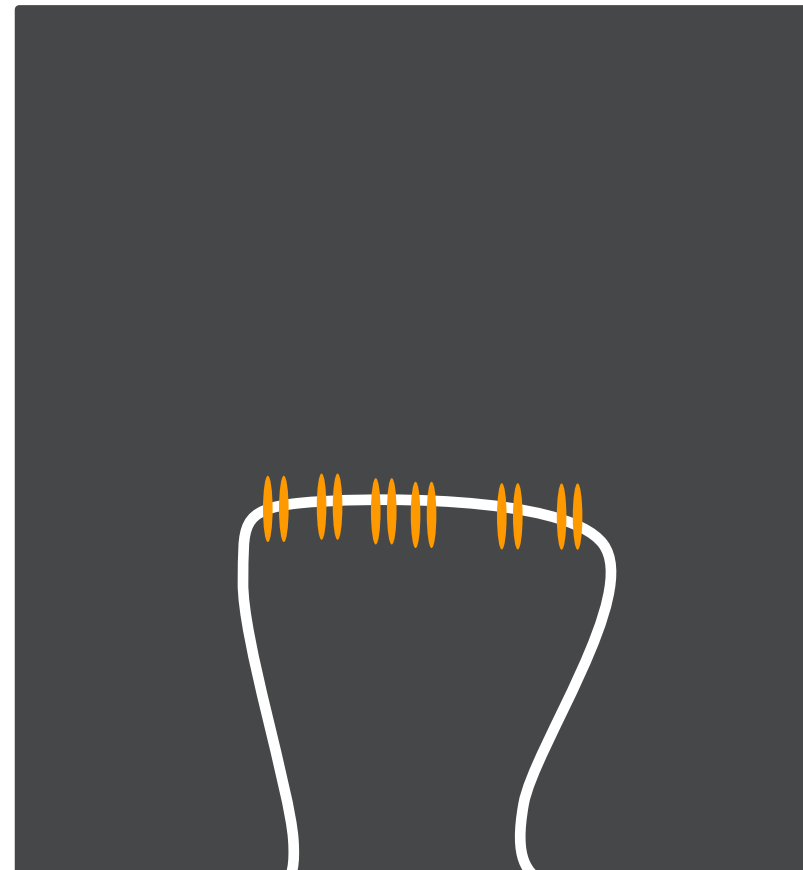
Later PD

- Postsynaptic concentration of dopamine in the striatum becomes closely linked to blood levels of levodopa
- Half life of levodopa in the blood: ~60-90 minutes



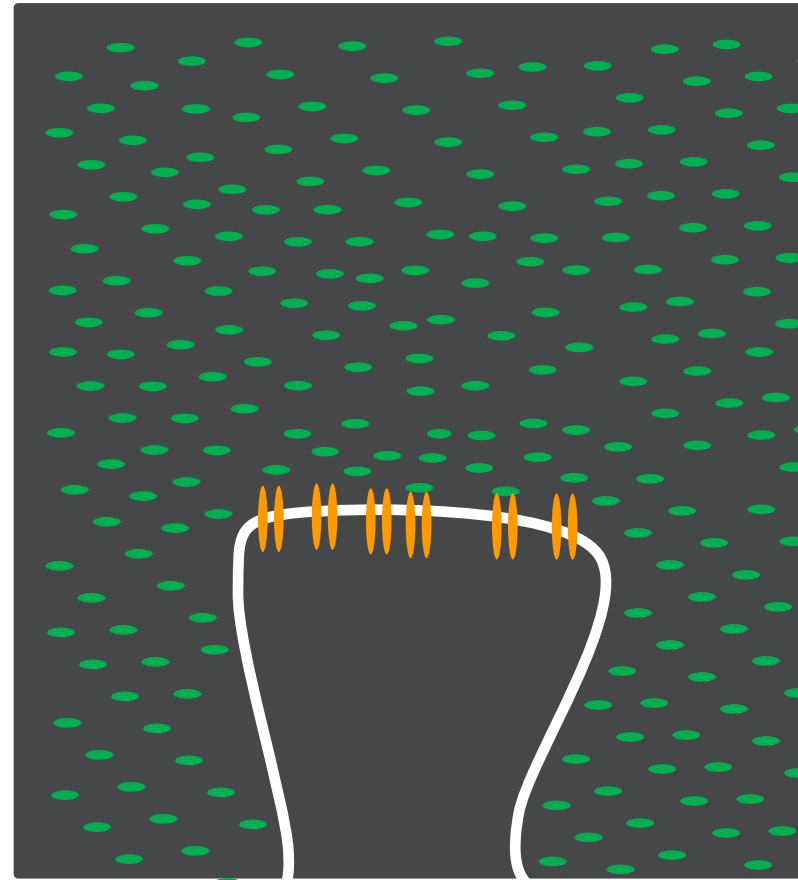
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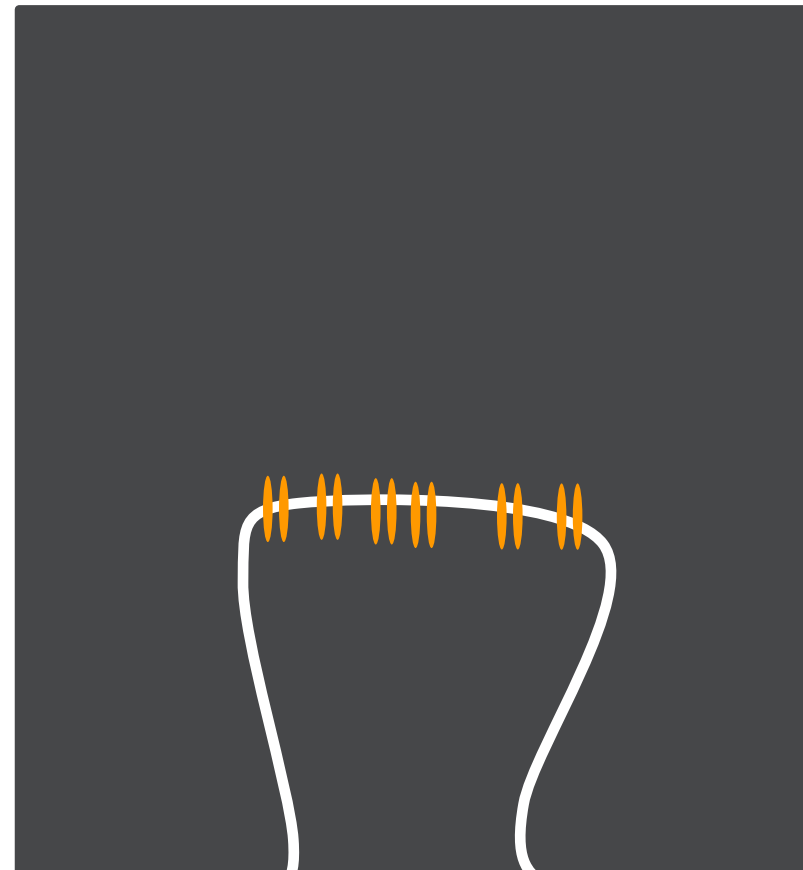
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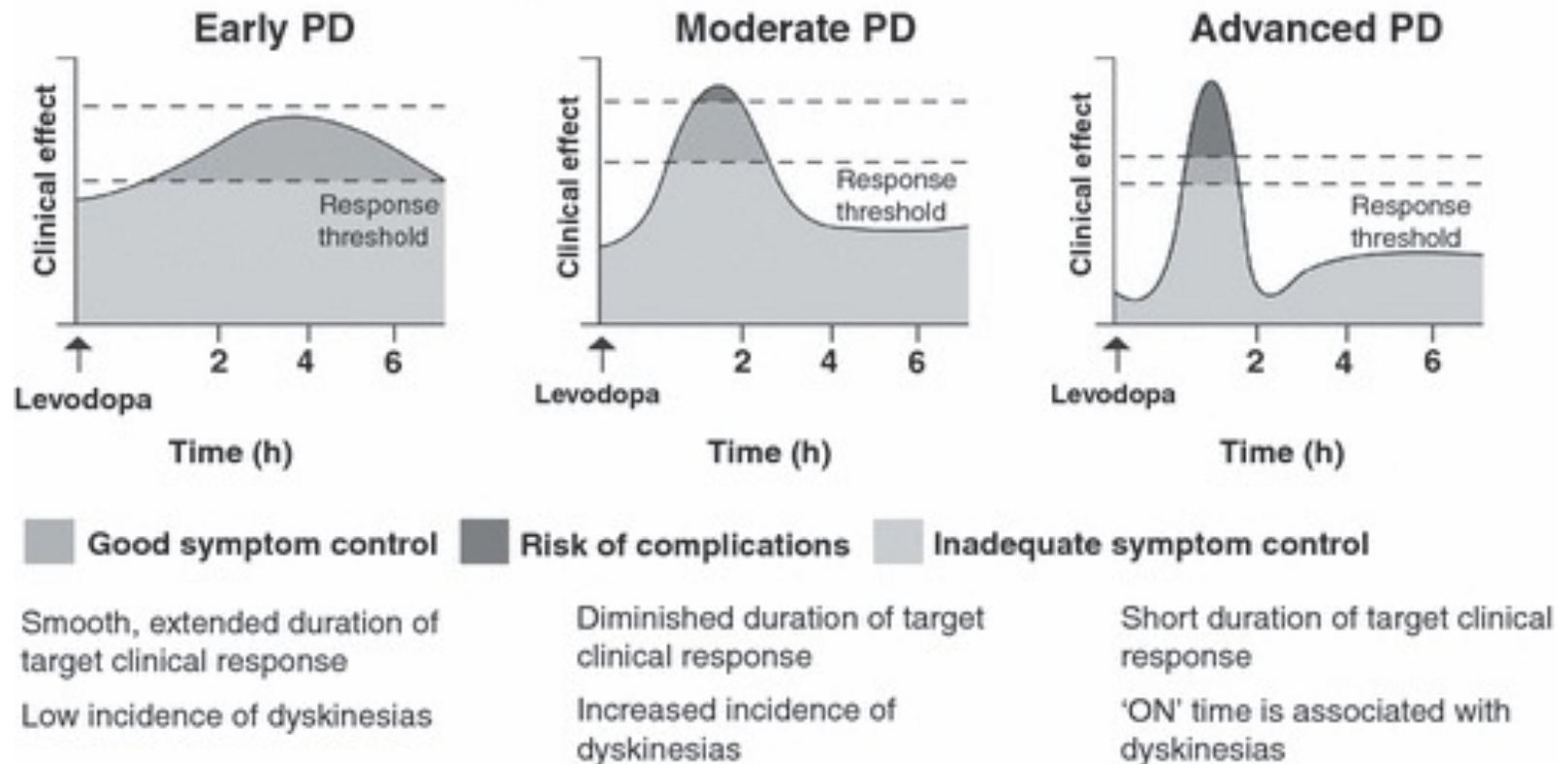


Later PD

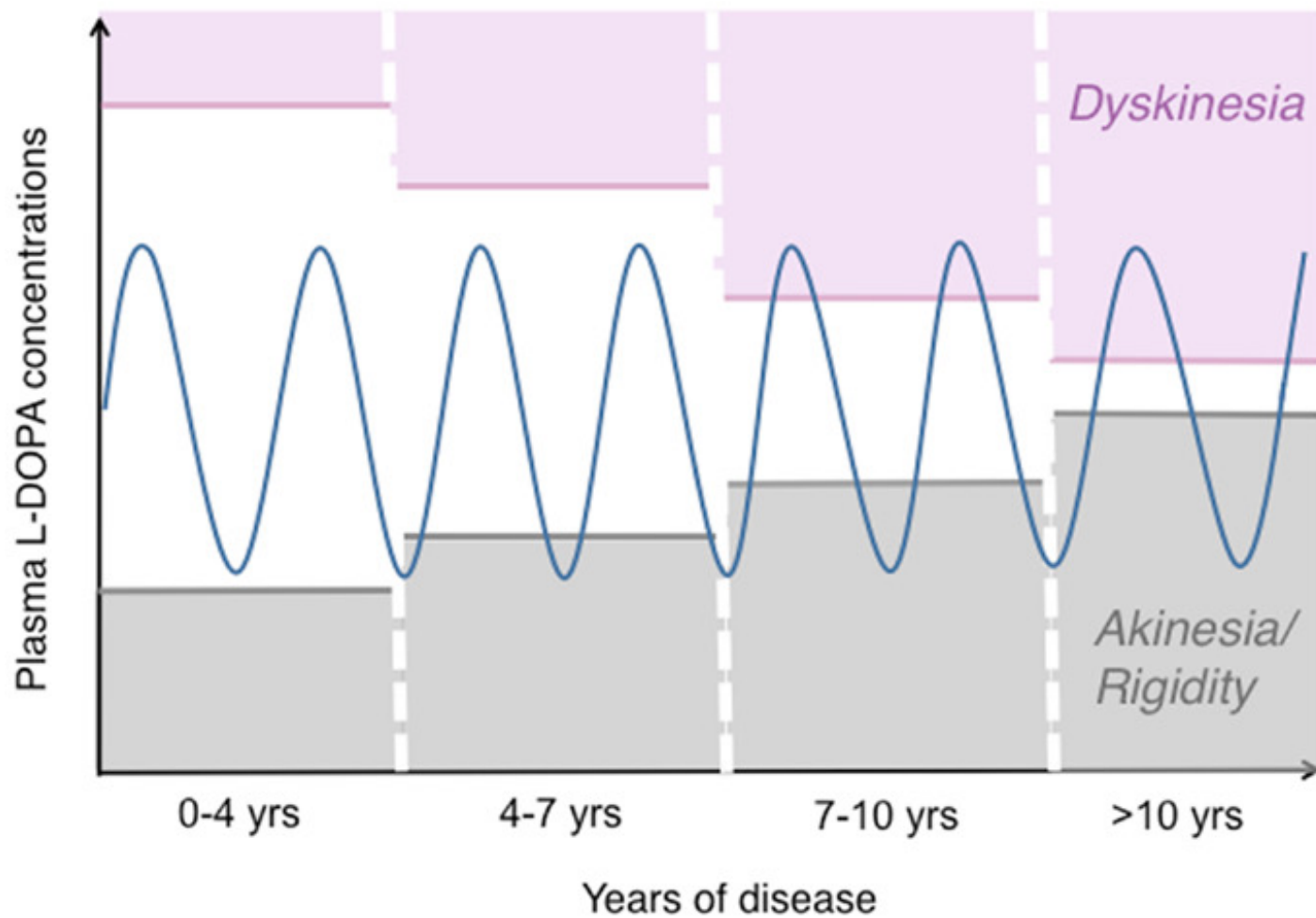
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Change in levodopa response over time



Schapira AH et al. *Eur J Neurol.* 2009;16(9):982-9.



Cenci MA. *Front Neurol.* 2014;15(5):424.

Adjunctive Medications for Motor Fluctuations

- Carbidopa levodopa ER 25/100 mg, 50/200 mg
- Pramipexole, Ropinirole, Rotigotine
- MAO-B inhibitors:
 - Rasagiline 1 mg (aka Azilect®)
 - Selegiline 5 mg twice daily
 - Safinamide (aka Xadago®) 50-100 mg daily

Adjunctive Medications for Motor Fluctuations

COMT inhibitors

- Entacapone (aka Comtan®)
 - 200 mg usually taken with each levodopa dose
 - Side effects: orange urine, diarrhea, rash, dyskinesias, other side effects of boosted levodopa dose
- Carbidopa-levodopa-entacapone (aka Stalevo®)
 - Combination tablet that comes in six different strengths
- Opicapone (aka Ongentys®) 50 mg taken at bedtime
- Tolcapone (aka Tasmar®) 100 mg

Adjunctive Medications for Motor Fluctuations

Rytary®

- Capsule contains beads of both immediate release and extended-release carbidopa levodopa
- 23.75/95 mg, 36.25/145mg, 48.75/195 mg, 61.25/245 mg

Adjunctive Medications for Motor Fluctuations

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- 23.75/95 mg, 36.25/145mg, 48.75/195 mg, 61.25/245 mg

Nourianz™ aka istradefylline

- 20 mg and 40 mg tablets – taken once daily
- Side effects: dyskinesia, insomnia/restlessness, nausea, constipation, dizziness, hallucinations

Medications to Suppress Dyskinesias

- **Amantadine** 100 mg one to three times daily
 - Suppresses dyskinesias, has modest effect on tremor, slowness, stiffness
- **Gocovri™** extended release amantadine capsules
 - 68.5 mg, 137 mg capsules taken at **bedtime**
 - 274 mg (2 capsules at bedtime) is the target dose
- **Osmolex-ER™** extended release amantadine tablets
 - 129 mg, 193 mg tablets taken in the **morning**
 - 322 mg is max daily dose
- **Possible side effects:** Dizziness, dry mouth, constipation, confusion, leg swelling, livedo reticularis, hallucinations

Other Medications

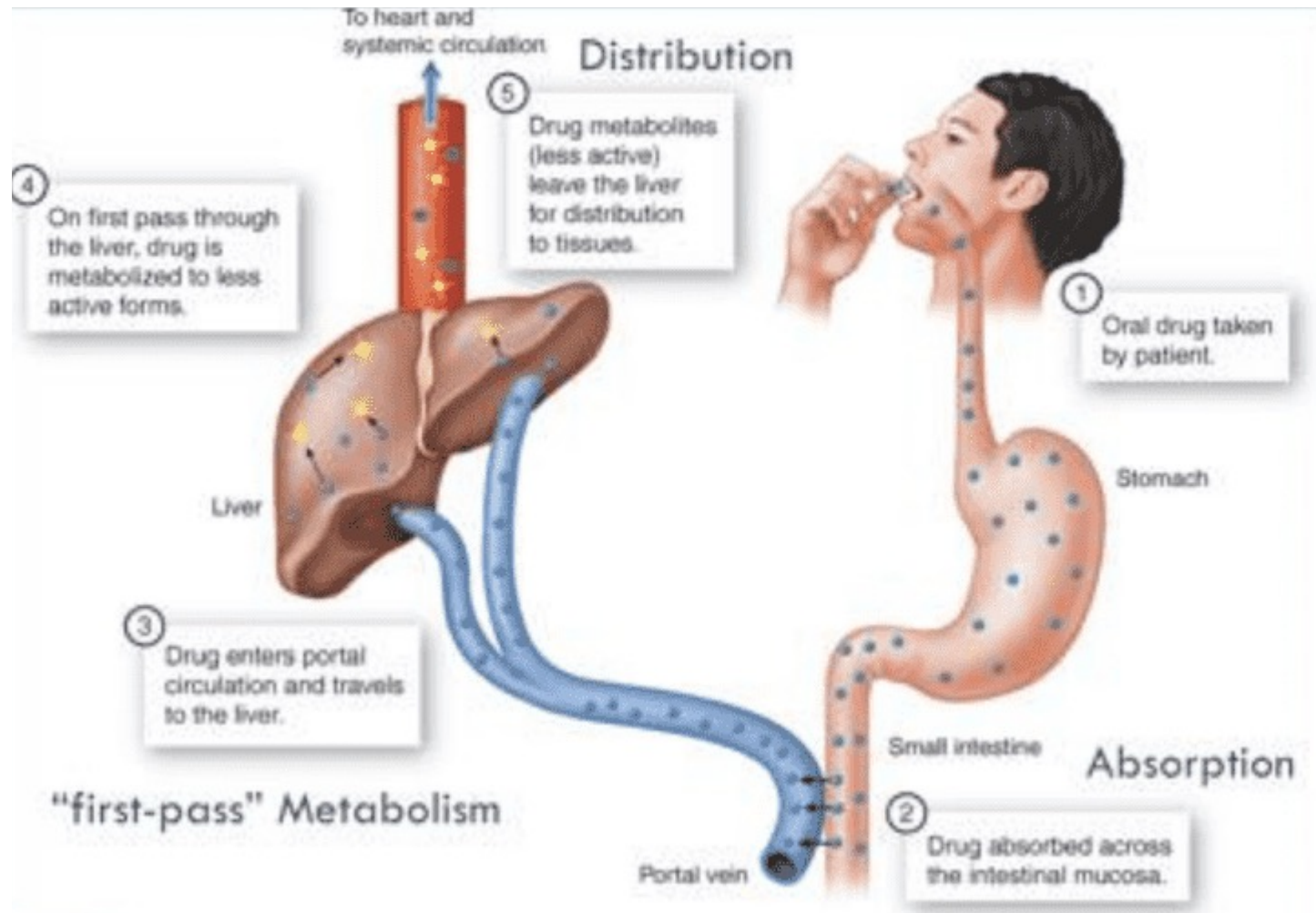
- Anticholinergic drugs: trihexyphenidyl, benztropine, biperiden
 - May help tremor and other motor symptoms of PD (particularly dystonia), but are almost always limited by side effects:

Side effects: dry mouth, worsened constipation, urine retention, dry eyes, confusion, forgetfulness, hallucinations, paranoia, drowsiness

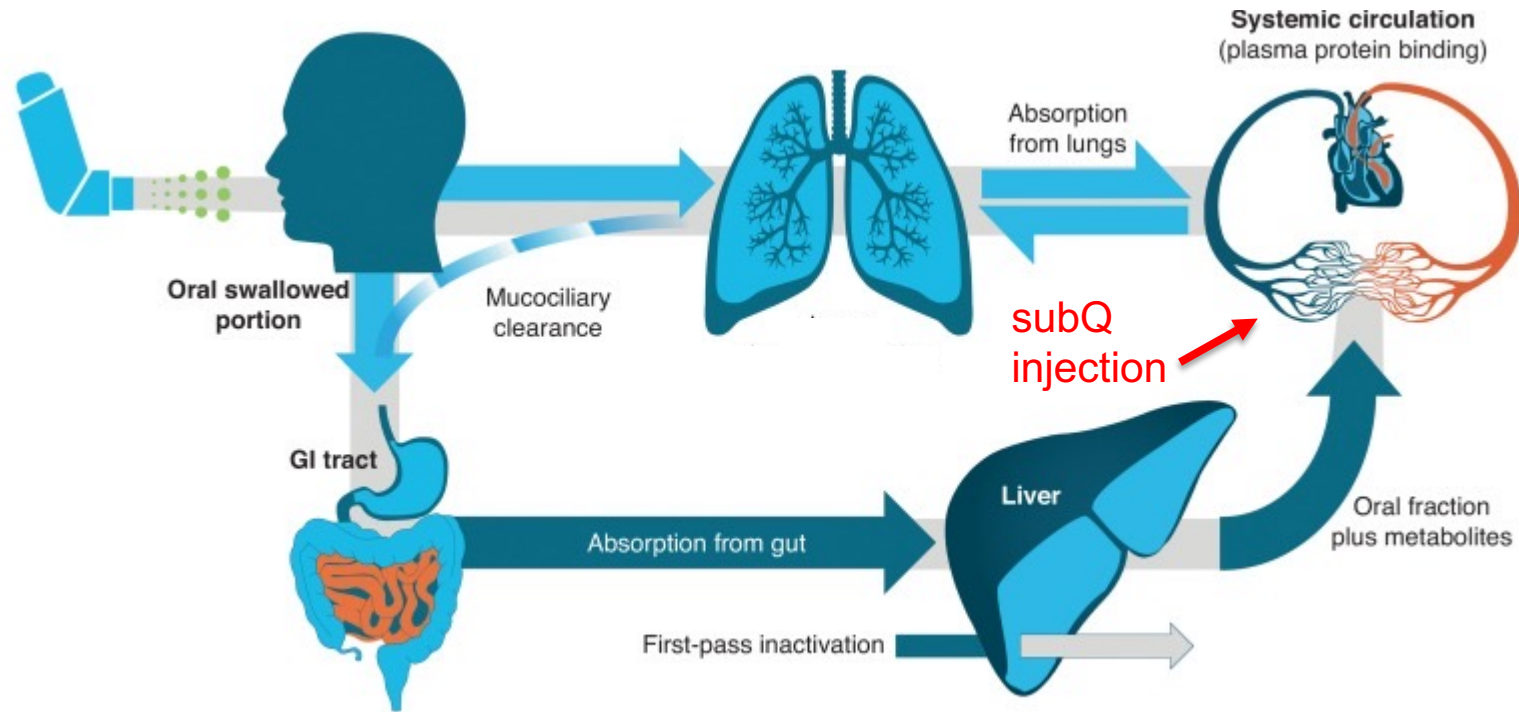
Rescue Medications for rapid wearing OFF

- Apokyn® subcutaneous apomorphine
- Kynmobi® sublingual apomorphine film
- Inbrija™ orally-inhaled levodopa capsules

Medicine taken by mouth



Medicine taken by inhaler or via the venous system



Strong P et al. *Drug Discovery Today*. 2019;23(10):1705-17.

Apokyn®

Subcutaneous apomorphine injector pen

Very fine (29 gauge) needle, similar to that used by patients with diabetes who require insulin injections

Easy-to-use dose dial



Replaceable multi-dose, 3-mL cartridges available through Specialty Pharmacy Providers

APOKYN Pen Pak Carrying Case



Side effects: nausea & vomiting (31%), sleepiness (35%), low blood pressure (11-18%), hallucinations/psychosis (14%), chest pain

Kynmobi®

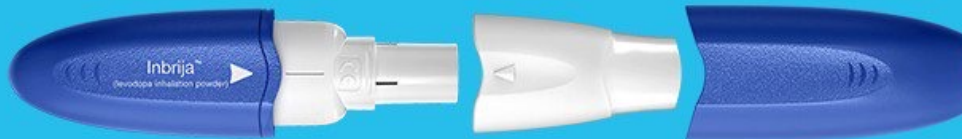
Sublingual apomorphine film



Inbrija™

Orally-inhaled levodopa

- 42 mg capsules (each dose is two capsules)
- Can take up to 5 doses daily



Inbrija™

Orally-inhaled levodopa

- 42 mg capsules (each dose is two capsules)
 - Can take up to 5 doses daily
-
- Possible side effects: Cough (15%), sputum discoloration, dyskinesias, nausea(2%), low blood pressure(2%)
 - Not recommended in patients with:
COPD, asthma, other chronic lung disease



Rescue Medications for rapid wearing OFF

- Apokyn® subcutaneous apomorphine
- Kynmobi® sublingual apomorphine film
- Inbrija™ orally-inhaled levodopa capsules

None of these contain carbidopa (the nausea blocker)

**Hopefully many more new PD
medications to come in the
near future**

Thank You!

