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WEXNER MEDICAL CENTER



Medications for Parkinson disease

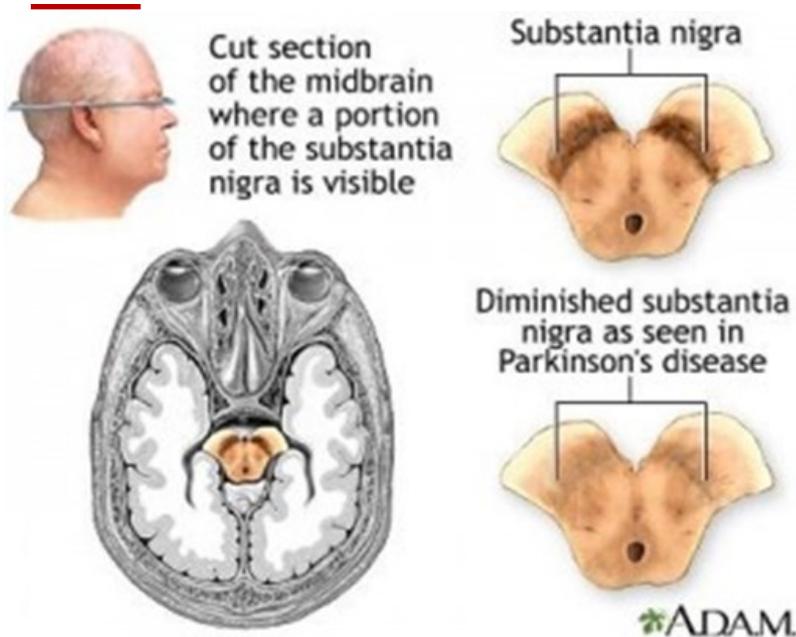
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Dopamine deficiency in Parkinson disease (PD)



We want to increase the dopamine in the brain of a patient with Parkinson disease

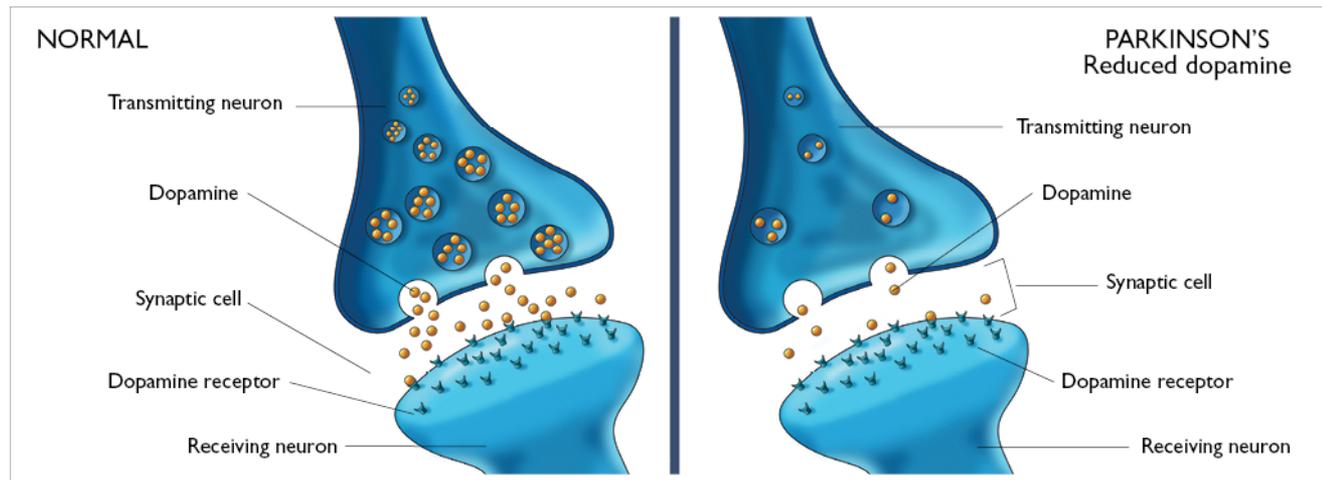


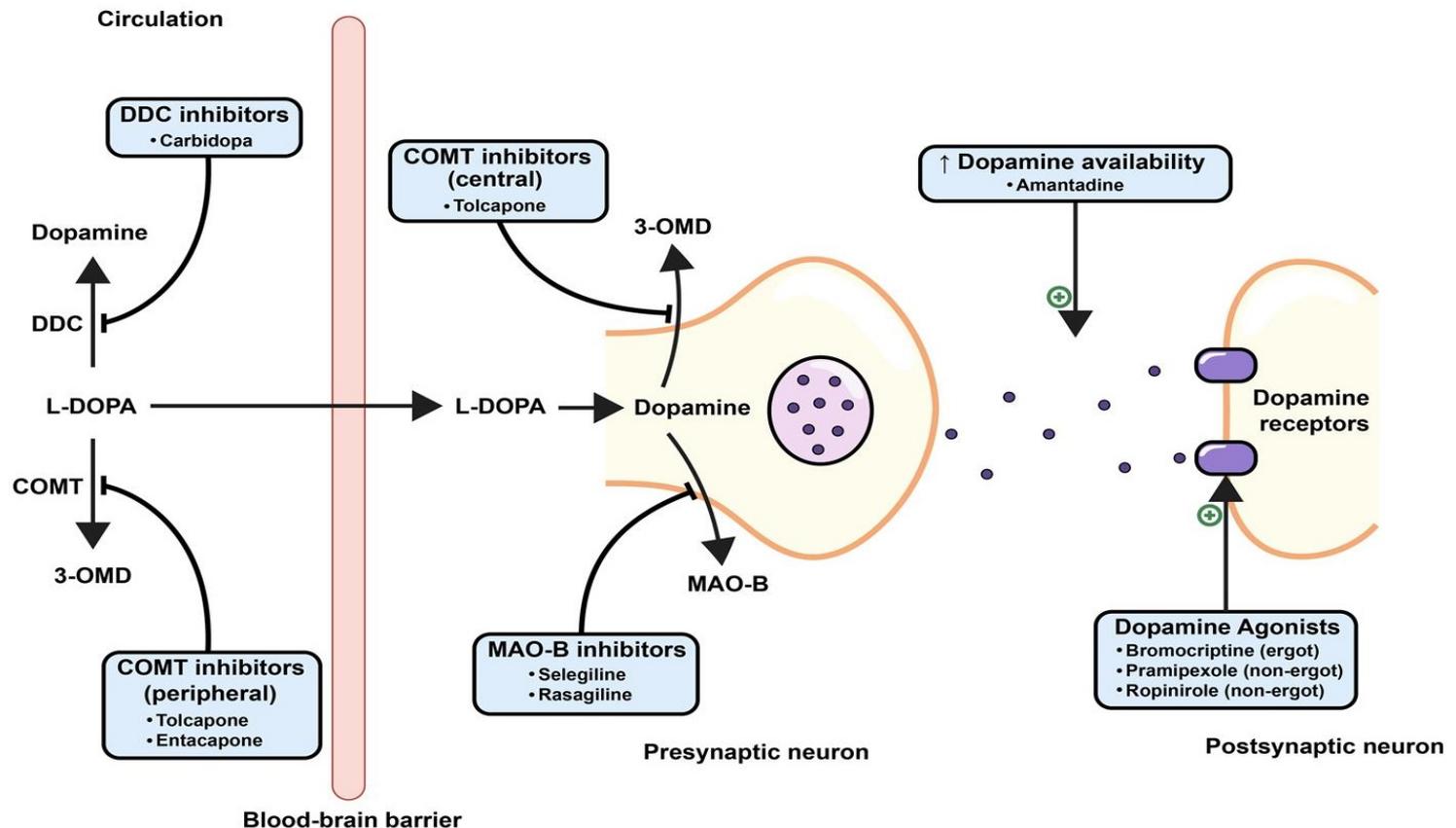
FIGURE 3. Illustration showing low levels of dopamine in a neuron affected by Parkinson's disease (right) and normal levels (left).

Images courtesy of

- <https://blog.nebula.org/is-parkinsons-genetic-nails-2019/>
- <https://www.ptglab.com/news/blog/the-neurochemistry-of-parkinsons-disease/>

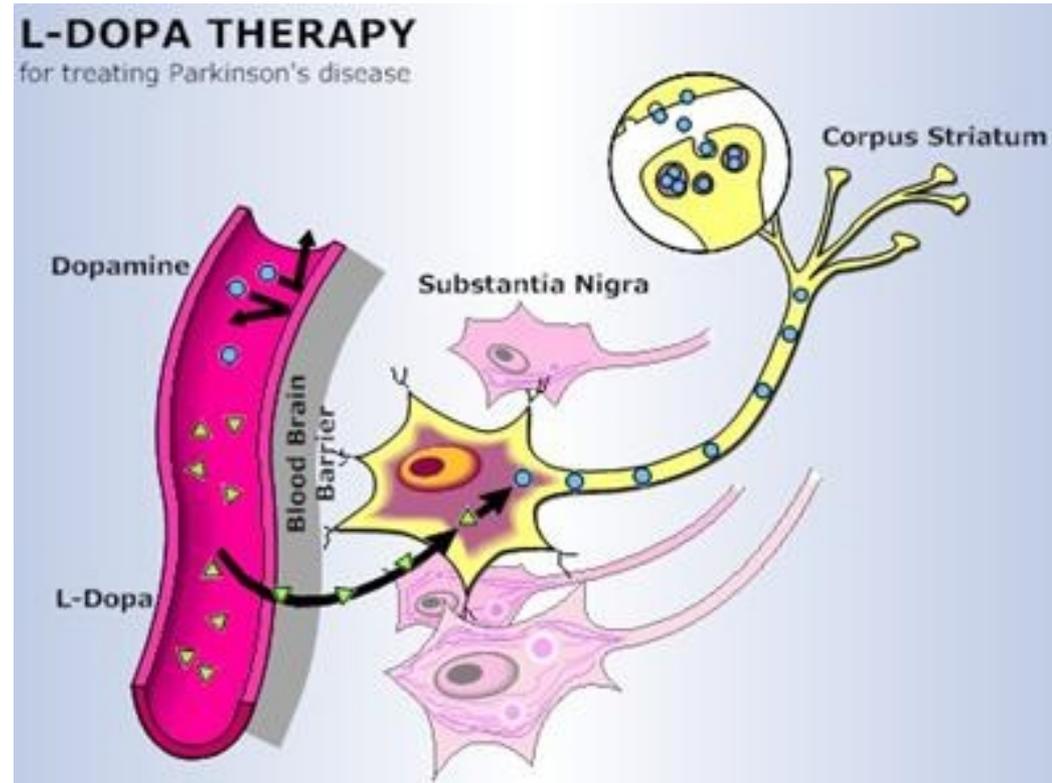
Replacing dopamine is mainstay of treatment

- Levodopa is converted to dopamine in the brain
- Dopamine agonists act like dopamine in the brain—MIMICS ITS EFFECTS
- Certain drugs block metabolism (breaking down) of dopamine in the brain, so it lasts longer in the brain



Levodopa is converted to dopamine in the brain

- Dopamine itself cannot cross into the brain
- Levodopa is a precursor to dopamine, meaning it can be chemically converted to dopamine
- Levodopa can cross into the brain from the bloodstream



Levodopa is always given with carbidopa

- Your medication is typically “carbidopa/levodopa” with a number after it: 25/100, 10/100, 25/250
- The first number is the amount (mg) of carbidopa in the pill
- The second number is the amount (mg) of levodopa in the pill—THIS IS THE IMPORTANT NUMBER, and is the drug of value
- Levodopa must get to the brain in order to work
- However, outside the brain, in the stomach and blood vessels, an chemical enzyme called “dopa decarboxylase” is trying to convert levodopa to dopamine. The dopamine outside the brain is useless to you. In fact, it can cause nausea and vomiting.
- Carbidopa blocks this enzyme dopa decarboxylase from converting levodopa to dopamine outside the brain. This allows more levodopa to get to the brain and be converted to dopamine there, where it can help PD symptoms



Carbidopa/levodopa comes in several forms

- Sinemet immediate release (pill)
- Sinemet controlled release (pill)
- Parcopa (pill that dissolves in the mouth)—THIS DOES NOT ACT ANY FASTER THAN THE SWALLOWED PILLS, just is easier in patients with swallowing problems
- Rytary —long acting oral capsule
- Stalevo (pill) = carbidopa/levodopa plus entacapone (a third drug) in one pill
- Duopa intestinal infusion (gel given through pump to small intestine)
- Inbrija (oral inhaler)

Sinemet IR and CR



- Cheap generic drug that is converted to dopamine
- Immediate release acts fairly quickly, within 20 minutes.
- Duration of benefit depends on the severity of your disease—2 hours in an advanced PD patient versus 6 hours in a patient with early disease
- Side effects: fatigue, lightheadedness, nausea, nightmares and at higher doses can cause hallucinations and dyskinesia
 - Dyskinesia are the extra dancing-like involuntary movements. These are from being OVER MEDICATED
- CR or SR formulation is a slow release.
 - The levodopa is infused with a polymer that must erode, and slowly delivers the drug into the gut
 - The problem is that in patients with constipation, the drug is broken down erratically or very slowly.
 - RESULT IS DELAYED OR ERRATIC KICKING IN
 - We tend to use this only at night in later stages of disease

Also CR is 2/3 to 90% of the potency of immediate release

Rytary is a newer long-acting levodopa, FDA approved in 2015

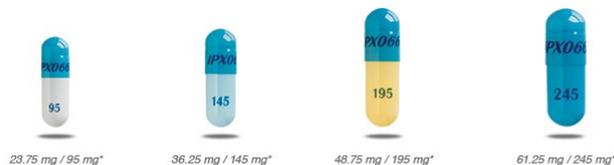
Capsule that contains beads which consist of two forms of levodopa—an immediate release levodopa and a long-acting levodopa. These beads are mixed together in the capsule

Typically take several capsules at once, between three to 5 times daily

Advantage is immediate kicking in but also long-acting levodopa, for consistent long dopamine levels in the brain

Used to treat “wearing off” when levodopa only lasts a short period of time by allowing levodopa to last longer, and with less abrupt wearing off

Can be expensive, but there is a patient assistance program



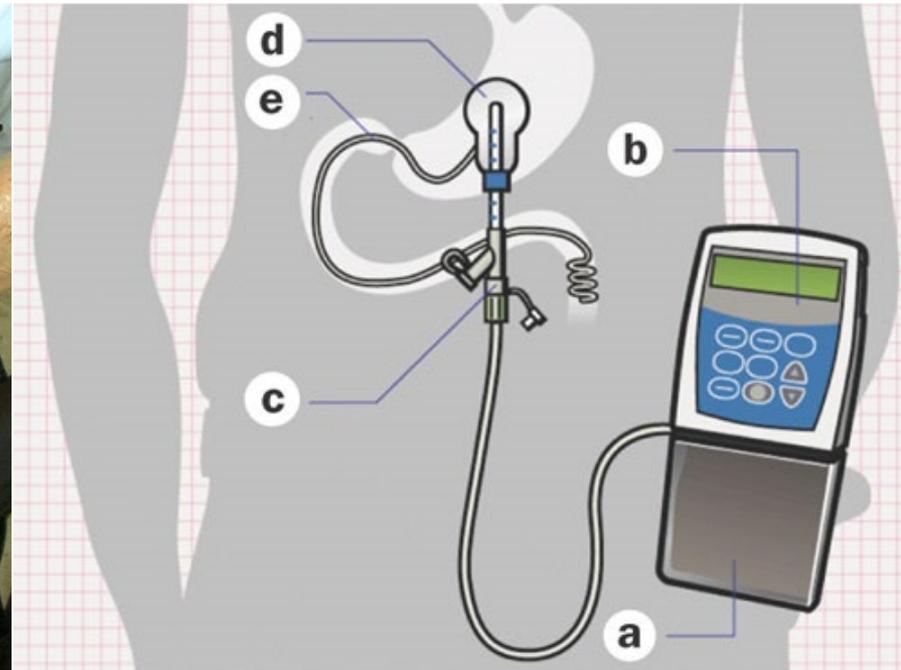
Capsules may not be representative of actual size.
*Carbidopa / levodopa.

Duopa intestinal infusion system

Duopa is a gel form of carbidopa/levodopa that is pushed through tubing through a hole in the stomach, into the jejunum, which is part of the small intestine

Requires a surgery to get a jejunum tube placed through the stomach “J tube”

Allows you to have infusion of levodopa into the gut every few minutes, for 16 hours per day.



Inbrija

Oral inhaler

Rescue therapy from off periods

Place a capsule into the inhaler and then place the inhaler into the mouth, to inhale a powder form of levodopa

The most common side effects of INBRIJA are cough, upper respiratory tract infection, nausea, and change in the color of saliva or spit.

Do not orally inhale more than 1 dose (2 capsules) for any OFF period. Do not take more than 5 doses (10 capsules) in a day.

Inbrija ™
(levodopa inhalation powder)
42 mg capsules



Dopamine agonists

These are drugs that mimic the effects of dopamine. They act on “dopamine receptors” which are on cells in the brain, just like dopamine would do

They resemble dopamine but aren't quite it

We tend to use these in early disease in persons younger than 70

Why? Not as strong as levodopa

However, side effects can be worse than levodopa, particularly in the elderly

Side effects

Nausea

Lightheadedness

Hallucinations

Leg swelling

Fatigue, more rarely sleep attacks

Advantages

Not associated with motor fluctuations

Long acting forms available



Dopamine agonist Apokyn, used for rescue

- Apomorphine is a strong agonist that is given subcutaneously as an injection under the skin, for rescue “off time”
- Requires determination of the effective dose to inject
 - This is done in the doctor’s office while monitoring for hypotension and getting baseline EKG
 - Injected 2 mg SQ then check standing and supine BPs before the injection, and again at 20, 40, 60 minutes
 - Requires to take a nausea medication chronically as apokyn nauseating
- Doses given through injection pen, kicks in within 10 minutes
- There is now a sublingual film formulation of apomorphine
 - Absorbed through the oral cavity
 - Kicks in within 30 minutes
- There is a trial for continuous subcutaneous apomorphine infusion underway

MOI-B inhibitors: selegiline, rasagiline, safinamide

- Decrease the degradation of dopamine in the brain by inhibiting the enzyme monoamine oxidase (MAO)
 - Dopamine is degraded in the brain as part of normal housekeeping
 - These drugs thwart that process to keep dopamine in the brain longer
 - They irreversibly stop the enzyme, and so effects last about 2 weeks
- We used to think these drugs had a risk of hypertension if you ate cheese or wine, but this is NOT true. This was true of an older generation of drugs that were not so specific to dopamine
- Side effects
 - Selegiline is the only one partly metabolized to amphetamine derivative and so may provide a bit stimulant effect
 - Generally well tolerated as milder drugs
 - May lead to potentiation of levodopa side effects (nausea, lightheadedness, dyskinesia)

COMT inhibitors

- Forms
 - Entacapone (given with Ldopa)
 - Opicapone (once daily drug)
 - Tolcapone (no longer used due to risk of liver injury)
- Stop the degradation of dopamine by blocking the enzyme catechol-O-methyl transferase (COMT)
- Side effects are those associated with potentiating levodopa
 - Nausea, lightheadedness, fatigue, nightmares, hallucinations, diarrhea
 - You may want to reduce your levodopa dose about 10 to 30% when starting these, to avoid dyskinesia
- Entacapone can make the urine orange (this is harmless)
- Stalevo is a combination pill containing carbidopa/levodopa and entacapone in ONE pill

amantadine

- Available in immediate release formulation in 100 mg tablets, or extended release once daily formulations (capsules or tablets)
 - IR can be two to three times daily
 - ER is once daily
- Useful for tremor, dystonia, and SUPPRESSES DYSKINESIA, also mild parkinsonian improvements
- This is cleared by the kidneys and so use caution in kidney disease
- Side effects
 - INSOMNIA: ALWAYS GIVE THE DOSES IN MORNING AND EARLY AFTERNOON AT LATEST
 - Hallucinations
 - Memory issues
 - Livedo reticularis (lacy rash, not dangerous)
 - Ankle edema (not dangerous)
 - Rare chance of corneal edema (get annual eye exam to monitor for this)
- Mechanism: increases dopamine release, blocks dopamine reuptake, stimulates receptors. NMDA receptor blocker

Anticholinergic drugs—trihexyphenidyl, benztropine

Trihexyphenidyl (Artane)

Start 1 mg BID, max 2 mg TID typically

Benztropine (Cogentin)

Start 0.5 mg BID, max 6 mg daily

Mechanism:

Aspiny neurons in striatum

Cholinergic interneurons preferentially form excitatory synapses onto striatal neurons of indirect pathway → block movement

Used for tremor and dystonia; no effect on slowness

Side effects

Poorly tolerated in elderly (worsen cognition)

Anticholinergic: dry mouth, constipation, urinary retention, exacerbate glaucoma

Option for young patients (<60 yo) with predominant resting tremor

Istradefylline or Nourianz



- An oral medication that works through novel mechanism
- A2A receptor antagonist
- Approved by the FDA in 2019 as an adjunctive (additional) medication to levodopa for “wearing off” symptoms
- Most common side effect is dyskinesia (about 12 to 13 percent of patients compared to 4% placebo)
- Other side effects: lightheadedness, constipation, nausea, hallucinations, insomnia
- Rare cases of impulse control disorders (lower the dose)
 - Disorders of risky behaviors for short term gain, long term negative consequences
 - Excessive gambling, drinking, smoking, shopping, hypersexual behaviors

Thank You



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