



Medications in Parkinson's Disease

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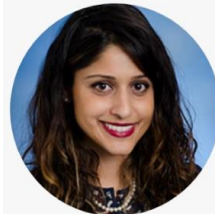
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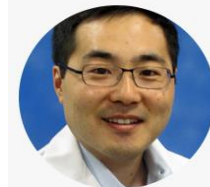
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Agenda

- Brief description on Parkinson's disease
- Medications & Therapies used in Parkinson's disease
- Symptom management in Parkinson's disease
- Upcoming treatments
- Q and A

What is Parkinson's disease?

- Second most common neurodegenerative disorder
- Estimated affecting 7 million people worldwide, will affect more than 14 million by 2040
- Average age of onset is 70 years
- Men affected more than women

Parkinson's Disease (PD)

- A clinical diagnosis: progressive neurodegenerative disorder characterized by several features including:
 - Bradykinesia / akinesia
 - Resting tremor
 - Muscle rigidity
 - Loss of postural reflexes
 - Flexed posture
 - Freezing of gait

Medications used for treatment in Parkinson's Disease

- Levodopa:
 - Restoration of dopamine in the brain
 - became available in 1960s
 - remains gold standard of medication treatment PD
- Adjunctive Medications include:
 - NMDA Receptor antagonist: Amantadine
 - MAO-B inhibitors: selegiline, rasagiline, safinamide
 - Dopamine agonists: pramipexole, ropinirole, rotigotine
 - COMT inhibitor: entacapone

Therapies used for treatment in Parkinson's Disease

- Deep Brain Stimulation (DBS):
- *Treatment for motor symptoms in appropriate patients.*
- DBS + Dopaminergic medications: effective long term therapy
- Exercise, Dance, and Rehabilitative Therapies → believed to help with brain neuro-plasticity

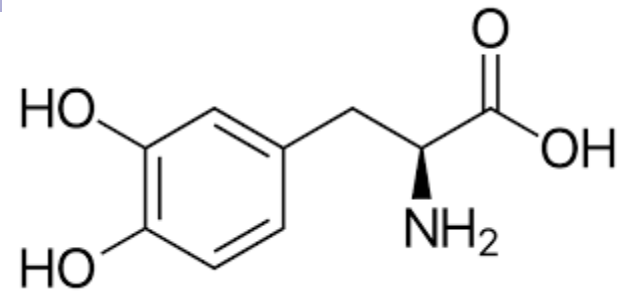
Movement Therapy & Parkinson's Disease

Recent evidence suggests that music-based movement therapy:

Improves: Gait
 Cognitive issues
 Quality of life

» M.J. de Dreu et al./Parkinsonism and Related Disorders 18S1 (2012) S114-S119

Levodopa Therapy



- Amino acid found in animals, plants (absorbed best on empty stomach)
- Remains among the most important advances in history of neurology.
- 1950's: Arvid Carlsson first showed that administering L-Dopa to animals with drug-induced Parkinson's caused a reduction in the animal's symptoms.
- 1960's: Oleh Hornykiewicz after finding greatly reduced levels of dopamine in autopsied brains of Parkinson's patients published with Walther Birkmayer dramatic therapeutic effects of IV administered L-Dopa to PD patients.

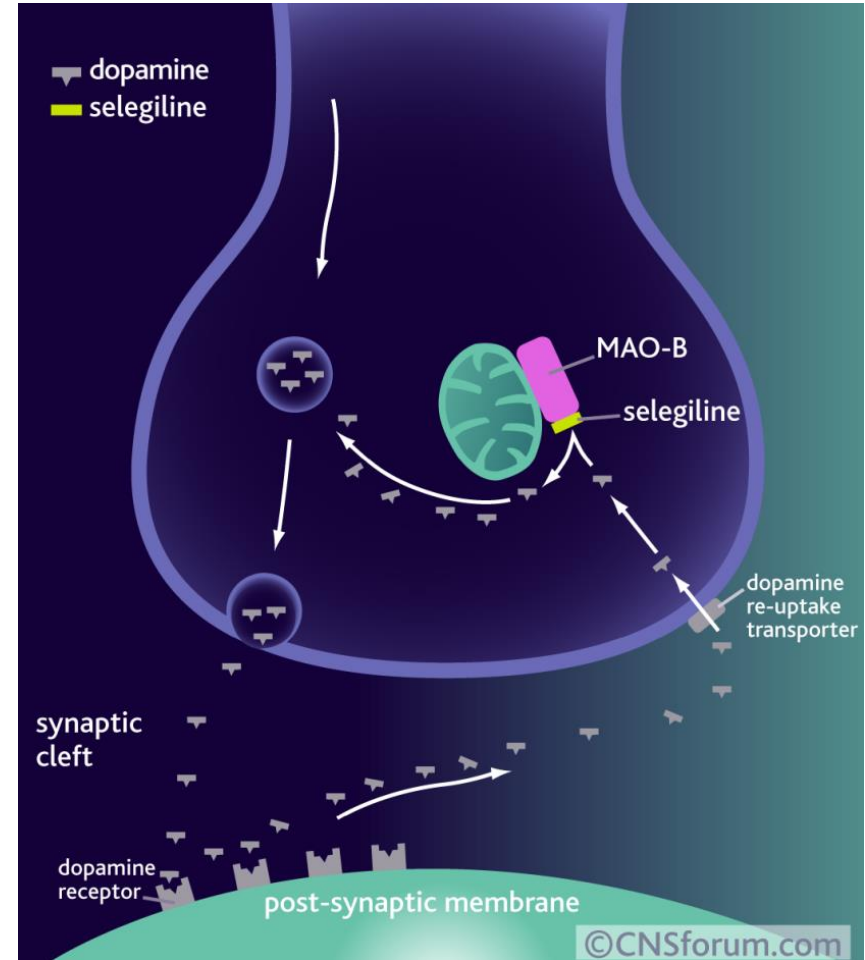
Levodopa therapy

- Helpful in treatment of motor symptoms. Initiation of medication is tailored to a person's symptoms and quality of life. Treatment: when symptoms impair activities of daily living.
- Slow initiation of medications (to avoid side effects)
- Side effects: nausea, vomiting, dizziness, drop in blood pressure, motor fluctuations, appearance of involuntary movements (dyskinesia)

Adjunctive Therapies: Medications that alter metabolism of levodopa (or dopamine)

MAO-B-Inhibitors:

- Selegiline
- Rasagiline
- Safinamide

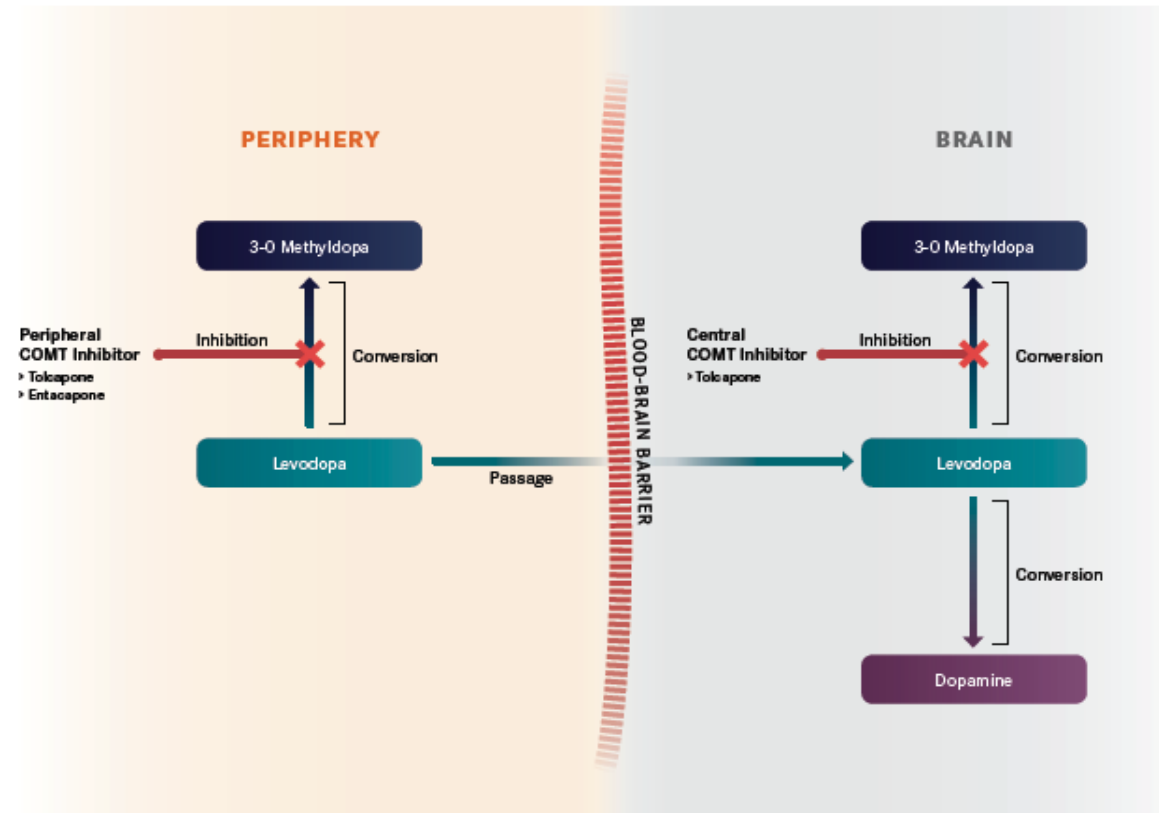


- **Side Effects:** caution in combination with SSRIs (used to treat anxiety) Enhance levodopa side effects

Adjunctive Therapies: Medications that alter metabolism of levodopa (or dopamine)

- COMT Inhibitor

FIGURE. COMT Pathway in the Brain



COMT indicates catechol-O-methyltransferase.
Source: Solla O, Cannas A, Marrosu F, et al. Therapeutic interventions and adjustments in the management of Parkinson disease: Role of combined carbidopa/levodopa/entacapone (Stalevo). *Neuropsych Dis Treat*. 2010;6(1):483-490.

- Side Effects: orange colored urine seen with entacapone, tolcapone not used associated with very serious liver toxicity

Medications that activate dopamine receptors:

- Dopamine Receptor Agonists:
 - Pramipexole, Ropinirole, Rotigotine (patch), Apomorphine (injection)
 - Bind and stimulate dopamine receptors
 - Usually less effective and more poorly tolerated than levodopa.
 - Require slow titration and slow tapering off.
- Side Effects: nausea, low blood pressure (orthostatic hypotension), hallucinations, peripheral swelling, excessive daytime sleepiness, and impulse control disorders (eg gambling/hypersexuality/excessive spending/excessive eating)

Other Medications

- NMDA receptor Antagonists: Amantadine
- Initially developed as an anti-viral medication.
- Mild benefit in tremor and also dyskinesias. (helps in hyperkinetic movements)
- Side Effects: peripheral edema, Livedo Reticularis (rash), insomnia, hallucinations, constipation, dry mouth, dry eyes, confusion, urinary retention –all worse in older adults.

Dent-Buyan, Laura; Mangin T, et al. Pharmaceutical Treatment of Parkinson's disease. Practical Neurology May 2018

TABLE. PHARMACEUTICAL TREATMENTS FOR MOTOR SYMPTOMS OF PARKINSON'S DISEASE			
ACTION	DRUGS	AVAILABLE FORMULATIONS	COMMON SIDE EFFECTS
Dopamine precursor with metabolic inhibitor	Levodopa/carbidopa	Tablets (IR, ER) Dissolving tablets	Nausea, vomiting, orthostatic hypotension, vivid dreams, hallucinations, delusions
MAO inhibitors reduce levodopa and dopamine degradation	Rasagiline	Tablets	Hypertension, orthostatic hypotension, potentiation of levodopa-related side effects
	Selegiline	Tablets, capsules, orally disintegrating tablets	
	Safinamide	Tablets	
COMT inhibitors reduce levodopa and dopamine degradation	Entacapone	Tablets	Potentiation of levodopa-related side effects, diarrhea, orange color of urine
	Tolcapone	Tablets	Potentiation of levodopa-related side effects, hepatotoxicity,
Dopamine receptor agonists	Pramipexole	Tablets, ER tablets	Nausea, vomiting, orthostatic hypotension, hallucinations, psychosis, impulse control disorders, peripheral edema
	Ropinirole	Tablets, ER tablets	
	Rotigotine	Transdermal patches	
	Apomorphine	Subcutaneous injection	
Other/Unknown	Anticholinergics (trihexyphenidyl, benztropine)	Tablets	Dry mouth, dry eyes, confusion, hallucinations, constipation, urinary retention
	Amantadine	Tablets, capsules, ER tablets	Dry mouth, dry eyes, livedo reticularis, confusion, hallucinations, constipation, urinary retention, peripheral edema

Abbreviations: COMT, catechol-o-methyltransferase; ER, extended release; IR, immediate release; MAO, monoamine oxidase.

Switch Gears!

- Symptom Management in Parkinson's disease

Treatment of Motor Symptoms:

- Motor Symptoms: Tremor/Rigidity/Bradykinesia
- 1st: add levodopa-adjust dose and/or frequency
- Available formulations: Standard release, sustained release, intestinal gel delivered into small intestine.
- If there is failure of symptoms (exception is tremor) to respond to levodopa ---this raises concern for atypical parkinsonian disorder.

Treatment of Motor Fluctuations:

- Why does this happen?
 - Progressive loss of dopamine producing neurons and changes in the dopamine receptor function produce syndrome of motor fluctuations, including early morning akinesia, wearing off benefit between doses, unpredictable OFF times, dyskinesia
- What can be done?
 - Medication adjustment including increase dose frequency, using adjunctive medications, using longer acting levodopa formulations, consideration of DBS.
- Who is a DBS candidate?
 - Has confirmed PD diagnosis for at least 4-5 years.
 - Person with atypical parkinsonian disorder is NOT a candidate.
 - Patient should be:
 - objectively, robustly responsive to levodopa
 - Evaluated by movement disorders specialist
 - Minimal neuropsychiatric issues
 - Normal MRI brain (no structural issues in the brain)

Treatment of L-Dopa-Resistant Motor signs:

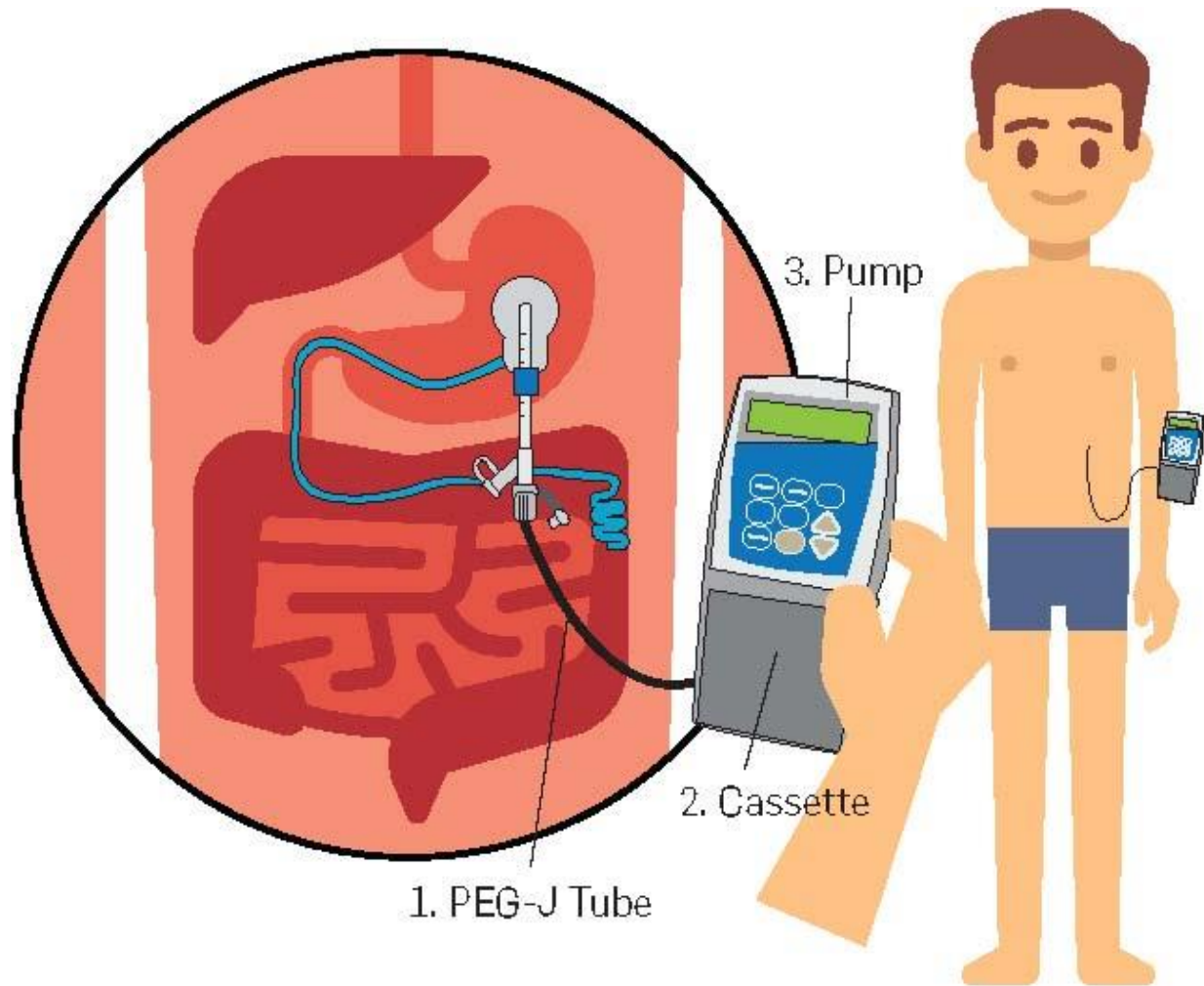
- Speech and Swallowing:
 - Despite optimal medications → requires a network of collaboration with speech and language therapists.
- Gait impairment/Postural Instability with falls/some Freezing of gait that is non-responsive to levodopa
 - rehabilitative therapies with Physical Therapy and Occupational Therapy
 - Exercise! 5 days a week, at least 30 minutes.
- Tremor that is resistant to L-dopa Therapy
 - May meet criteria for Deep Brain Stimulation treatment

Treating Nonmotor symptoms in Parkinson's Disease:

- Low Blood Pressure (orthostatic hypotension)
- Constipation (Gastrointestinal dysfunction)
- Drooling
- Frequent Urination (involved urology)
- Neuropsychiatric: Depression/Anxiety/Apathy/Cognitive Dysfunction/ Hallucinations

Newer Treatments on Motor Fluctuations in PD

- Duopa (levodopa enteral suspension)



www.parkinson.org/Understanding-Parkinsons/Treatment/Surgical-Treatment-Options/Duopa

Newer Treatments on Motor Fluctuations in PD

- Levodopa Inhaler for OFF periods.



Newer Treatments on Motor Fluctuations in PD

- Istradefylline (Adenosine A_{2A} receptor inhibitor) aka known as NOURIANZ™ is indicated as adjunctive treatment.
- GOCOVRI® (long-acting amantadine) extended release capsules—for dyskinesia in PD patients treated with levodopa therapy.
- ONGENTYS® (opicapone) capsules-adjunctive treatment to levodopa therapy in patients with PD experiencing “off” episodes.

Newer Treatments on Motor Fluctuations in PD

- Apomorphine Sublingual aka KYNMOBI™
(apomorphine hydrochloride)
- Sublingual film is a prescription medicine used to treat short-term (acute), intermittent OFF episodes
- Available September 2020

Summary

- No cure yet for Parkinson's disease.
- BUT significant treatments are available!
- No medications that lead modify the progression of the disease.
- BUT we believe that exercise does has neuroprotective effects.

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