THERAPIES IN PARKINSON'S DISEASE

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Peak Neurology

Colorado Springs Parkinson's Support Group: July 6th, 2024

Disclosure

NO CONFLICTS OF INTEREST

VIEWS EXPRESSED ARE OF MY OWN

AND DO NOT NECESSARILY REFLECT THE VIEWS OR POSITIONS OF ANY ENTITIES I REPRESENT

Your Parkinson's Pharmacist

- 2013 Doctorate of Pharmacy – Butler University
- PGY1 and PGY2 Pharmacy Residencies; Board Certified
- 2015-2019 Primary Care Clinics– Ft. Carson
- Parkinson's and Movement Disorder Center – University of Kansas
- 2022 Peak Neurology – Colorado Springs

Peak Neurology

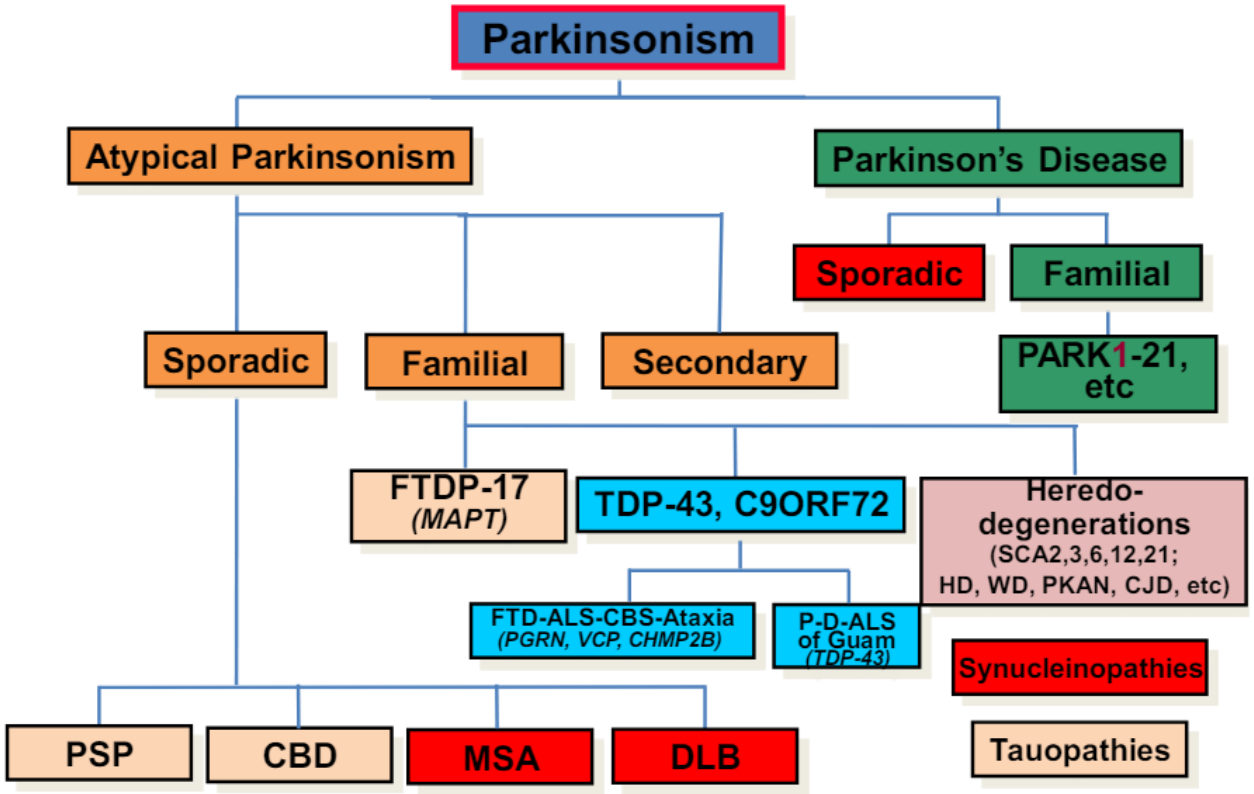
Parkinson's Foundation

Your Parkinson's Pharmacist

- Collaborate with your care team to manage
  - Movement symptoms
  - Non-Movement symptoms
- Education: Parkinson's and medications
- Non-medication and Medication adjustments
- Medication Reviews
- Drug-Drug Interactions
- Resource for patients and providers

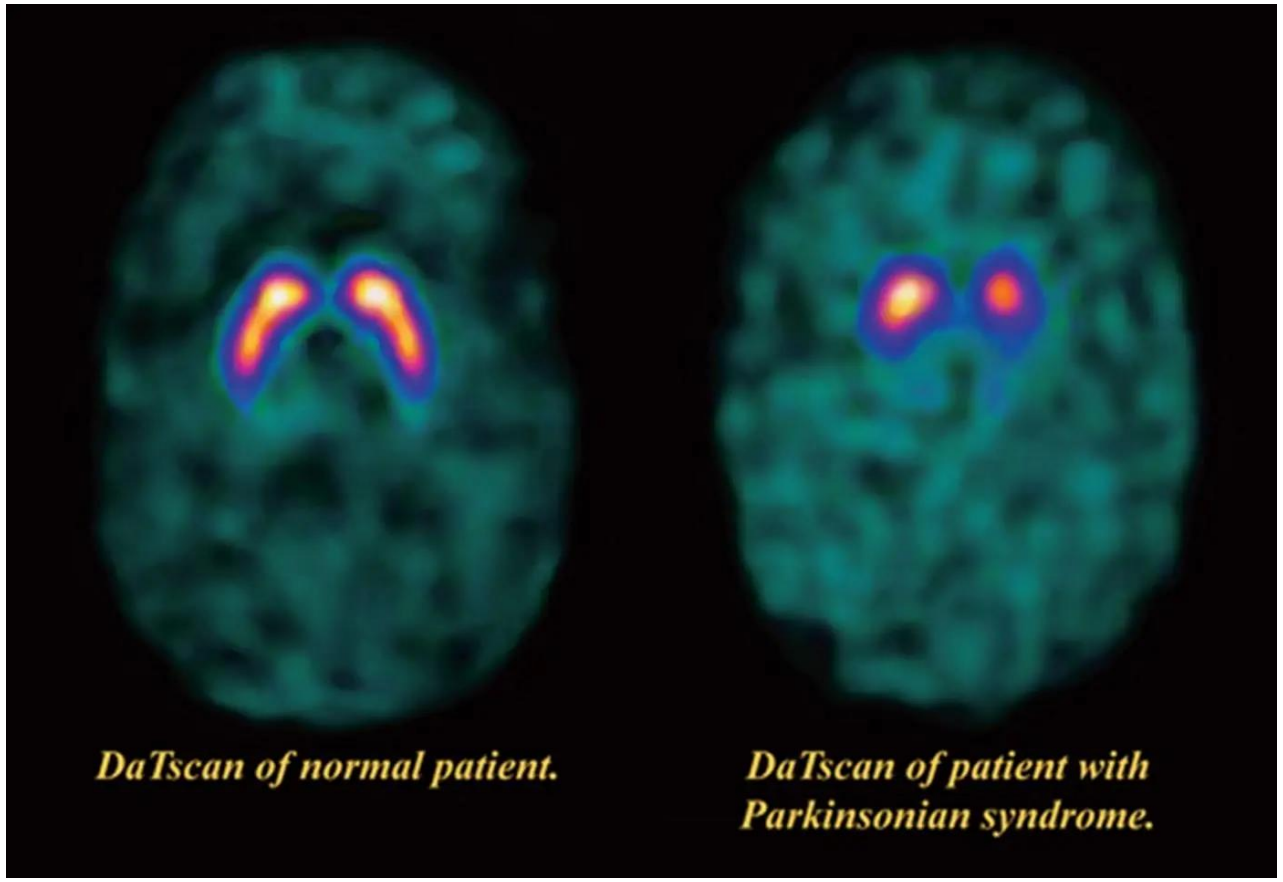
Outline of Presentation

- Brief Intro of Parkinson's Disease
- Basic Principles and Expectations of Therapies
- FAQs
- Therapies on the Horizon
- Q & A



Jankovic. Lancet Neurol 2008;7:9-11
Lindquist et al. Clin Genet 2013;83:279-83
http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab

PARKINSONISM VS. PARKINSON DISEASE



[Parkinson's Foundation; https://www.parkinson.org/understanding-parkinsons]

Dopamine Deficiency in the Brain

- Substantia Nigra center of the Brain
- ~50% of Dopamine Neurons Lost by time of Diagnosis

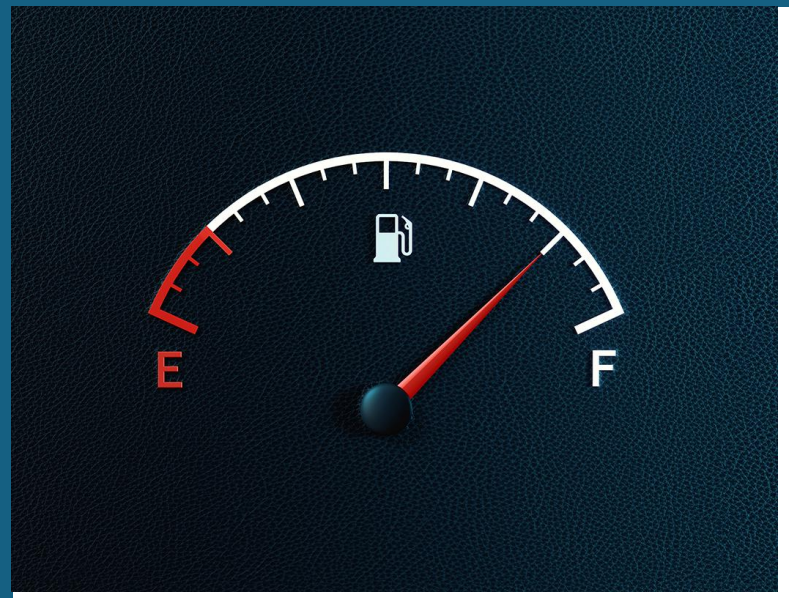
Parkinson's Disease is Levodopa-Responsive

Significant and Sustained Response = Parkinson's Disease

- "Slow and Small Movements" Bradykinesia
- Stiffness / Rigidity
- Rest Tremor – Sometimes Responds

Parkinsonisms

- Do NOT Respond or Small Degree
- Lose Response (ex. After 1-5 years)



Progression and Levodopa

Early Parkinson's

- Dopamine Reserve
- Doses Last 6 hours

Advanced Parkinson's

- Running on Fumes
- 90 min Levodopa half-life

OFF time

"Slow and Small"

Shuffling Walk

Tremor

Dystonia - painful spasm

Dyskinesia

Random Movements

Jerky

Wiggly

Dance like

Movement
OFF time vs. Dyskinesia

Non-Movement OFF Time

Non-movement Symptoms of Parkinson's

Neuropsychiatric
• Depression • Anxiety • Apathy • Psychosis • Dementia • Cognitive Impairment

Autonomic Dysfunction
• Drooling • Orthostasis • Blood pressure changes • Urinary Dysfunction • Erectile Dysfunction • **Constipation** • Excessive Sweating

Non-movement Symptoms of Parkinson's

Sleep and Wakefulness

- **REM Sleep Behavior Disorder**
- Sleep fragmentation
- Insomnia
- Excessive Daytime Sleepiness

Other

- Pain, Neuropathy
- Fatigue
- Sense of Smell
- Eye dysfunction

Your Parkinson's Team

Approaches to Care

Prevention	• Preventing the disease
Disease Modification	• Stopping or Slowing Progression • Reversing the Disease
Symptomatic Treatment	• Improving Quality of Life

Approaches to Care: Parkinson's in 2024

~~Prevention~~

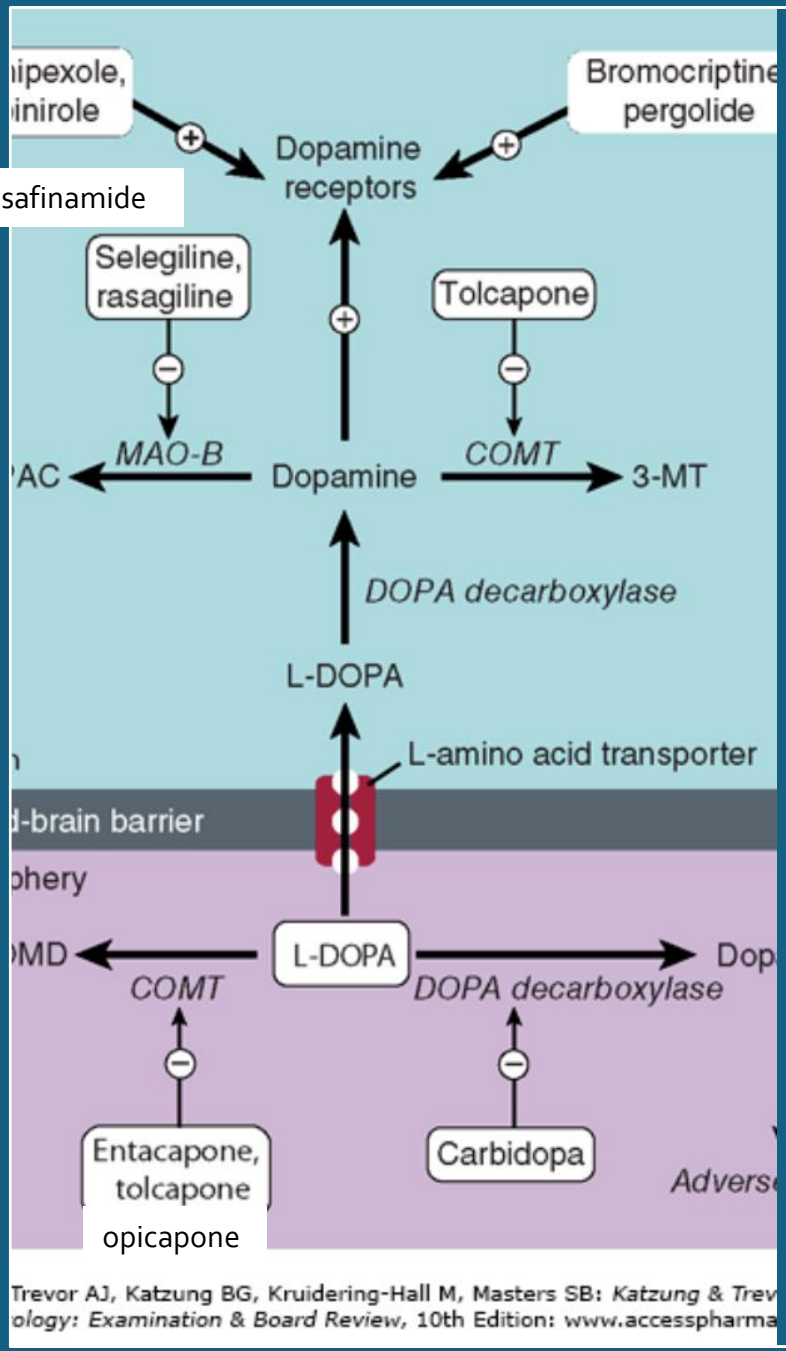
Exercise 150+ mins/week
(Cardio, Resistance, Mobility)

Disease Modification

- **Exercise** to slow progression
- No pill or supplement currently

Symptomatic Treatment

- Medication
- Non-Medication Therapies



Medication: Levodopa

- **Converted to Dopamine**; Protected by Carbidopa

-**Most Potent for Movement symptoms**:

-- Slow and small movements, Rigidity

--Tremor (sometimes responds)

Carbidopa/levodopa (Sinemet) IR tablet, DHIVY

Carbidopa/levodopa (Sinemet CR) ER TABLET

Carbidopa-levodopa (RYTARY) ER capsule

Carbidopa-levodopa intestinal gel (DUOPA)

Inhaled levodopa (INBRIJA)

Medication for Movement Symptoms

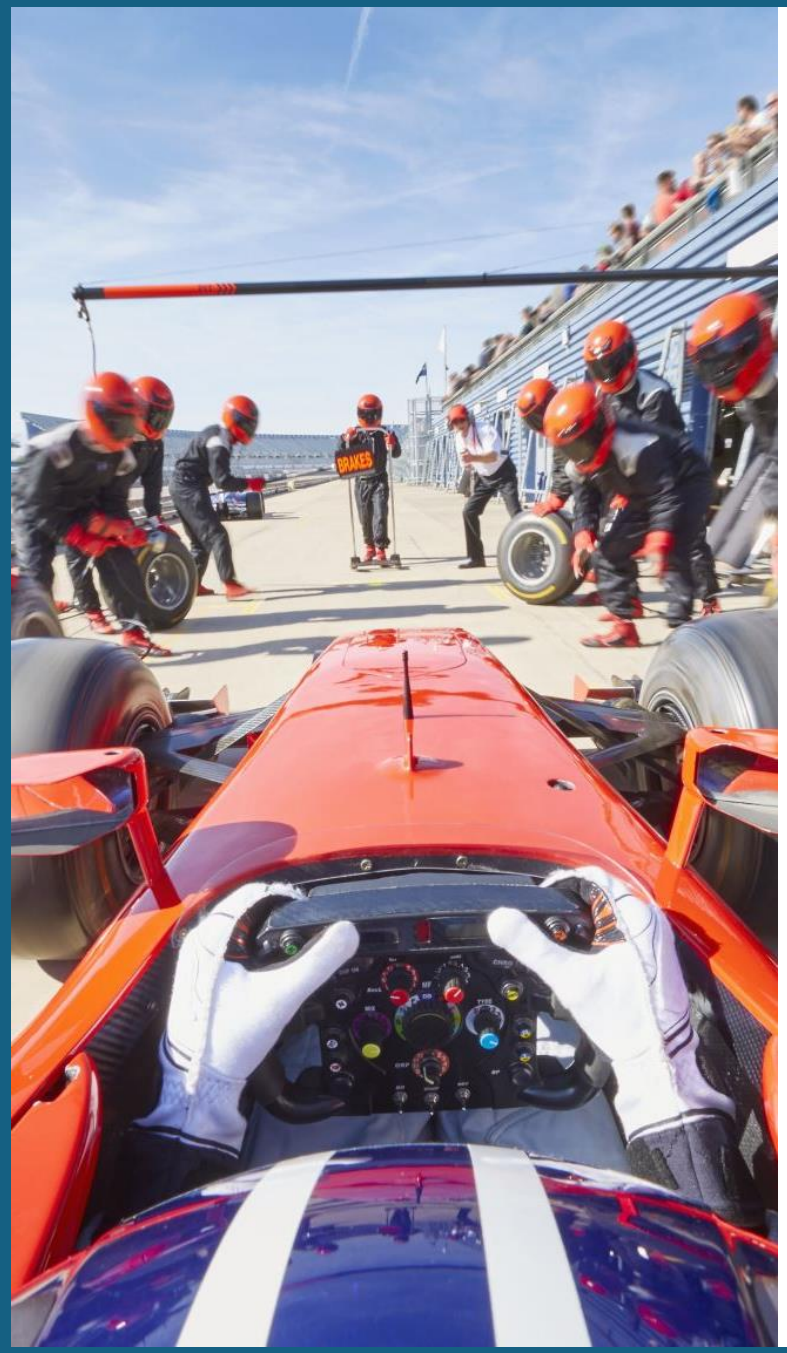
Levodopa 'Boosters'	Dopamine 'Boosters'	Dopamine mimics	Others
• Entacapone • Opicapone	• Rasagiline • Selegiline • Safinamide	• Apomorphine • Pramipexole • Ropinirole • Rotigotine patch	• Amantadine • Anticholinergics (Trihexyphenidyl) • Istradefylline

Levodopa vs. Dopamine mimics/boosters

	Levodopa	Dopamine Mimics & Dopamine Boosters
Effect on Movement	**Stronger**	Weaker
Dyskinesia	Higher risk	Lower Risk
Dopamine Side Effects	**Lower risk**	**Higher Risk**

Dopamine side effects

- Nausea/Vomiting
- Blood pressure drop --> falls
- Hallucinations
- Constipation
- Impulse Control disorders
- Cognitive impair, Sleepiness



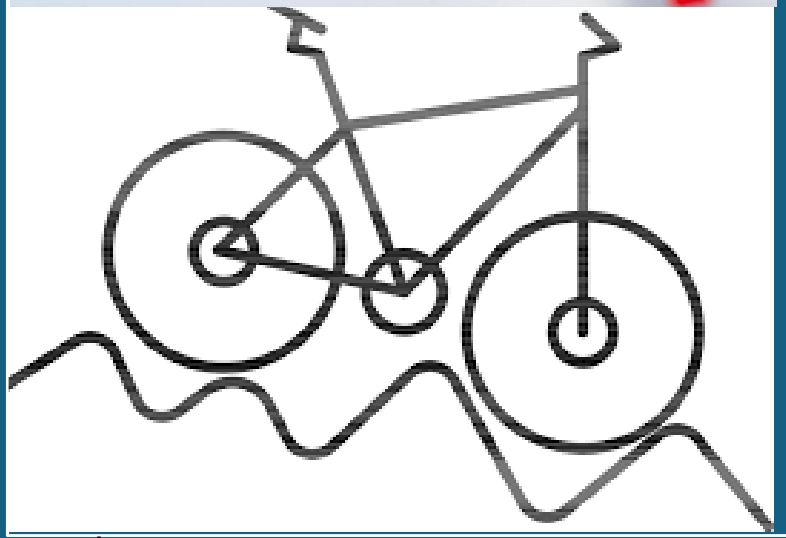
Motor "On-Off" Fluctuations

- Random OFF time
- Wearing OFF Dyskinesias
- Delayed ON

Stomach

Blood

Brain



Motor "On-Off" Fluctuations

Medication Absorption Failure

-Constipation, Slow moving Gut, Food, Drugs

No, Partial, or Delayed ON

Progression of Parkinson's

Less ability for brain to "Buffer" dopamine

Wearing OFF Dyskinesias

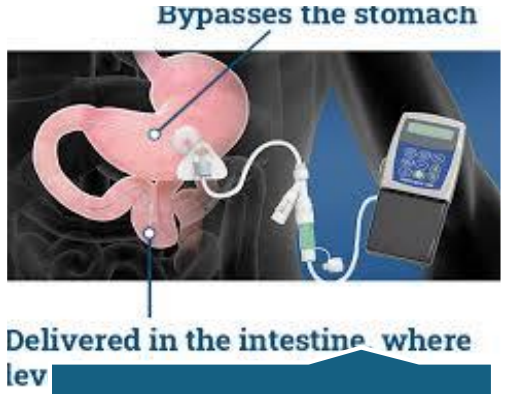
Loss of "Shock Absorbers"

vecteezy.com

Motor Fluctuations: Treatments

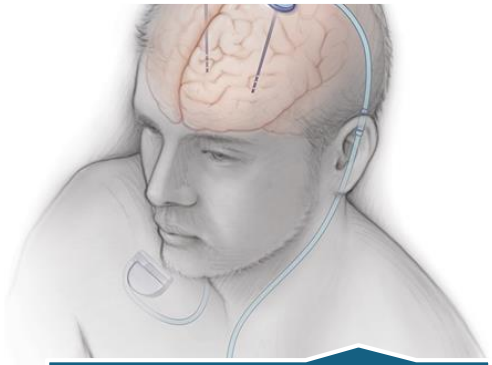
APOKYN injection

INBRIJA inhaler



DUOPA

Rotigotine Patch



Deep Brain Stimulation (DBS)

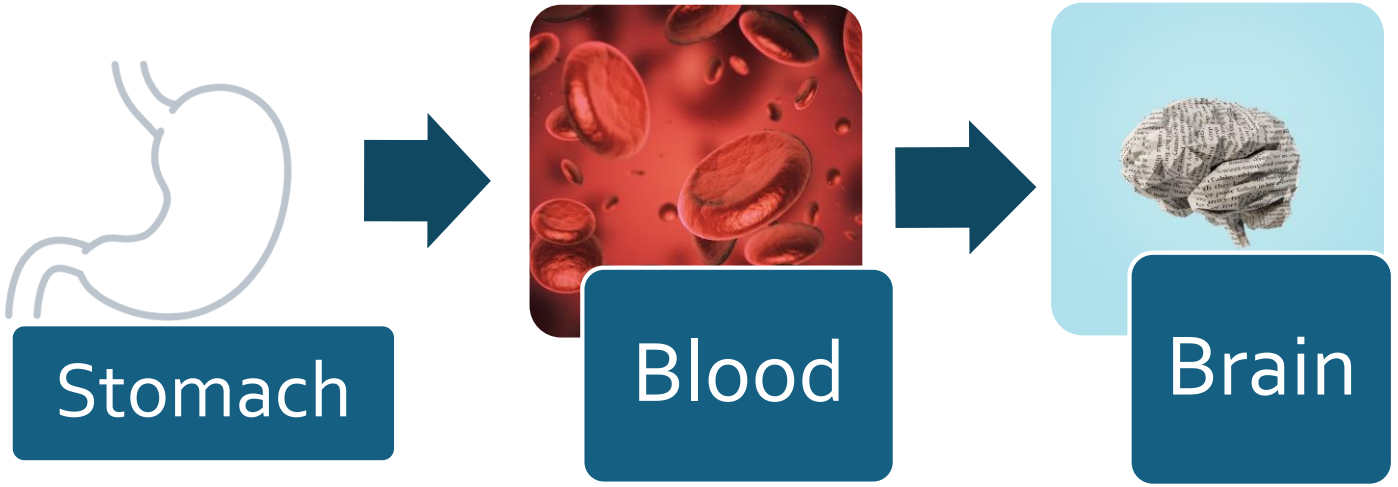
Lesioning (ex. MgFUS)

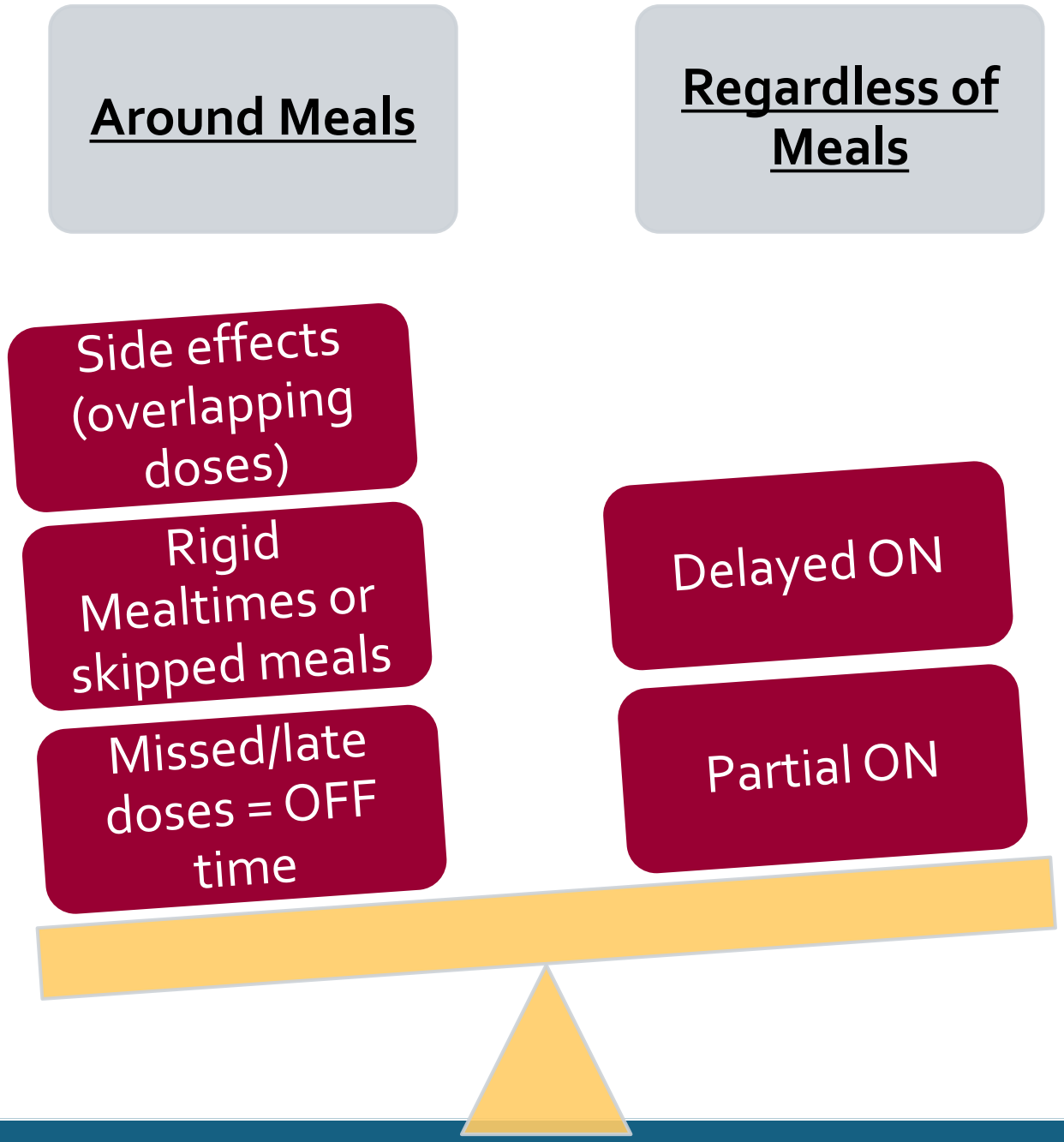
Protein and Levodopa = Nuanced

- **Amino Acids (Protein) Compete with Levodopa**
  - Across Gut Wall → Take 30-60 mins before meal
  - Across Blood Brain Barrier → Cannot escape this
    - Half-life of amino acids minutes to several hours

"4x4 Rule"

- **If Levodopa 4+ doses/day or doses within 4 hrs; take regardless of food**
  - Can always adjust dose, use therapies for Motor fluctuations





Protein and Levodopa = Nuanced

Do NOT reduce protein intake

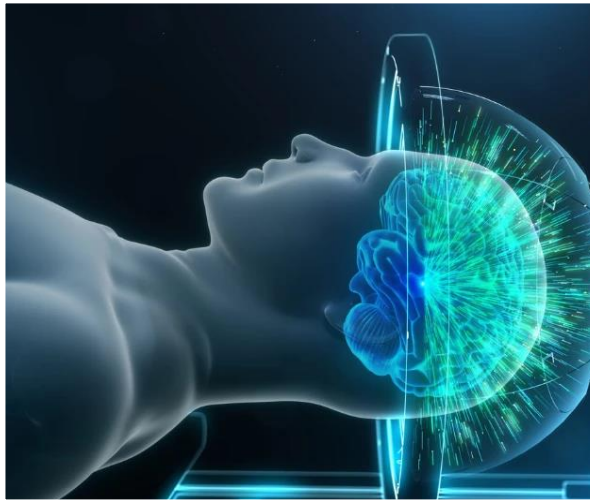
- Risk of muscle wasting

- Consider high protein intake at dinner and/or bedtime

Surgical Therapies for Parkinson's Disease

DBS

Deep Brain Stimulation



Lesioning

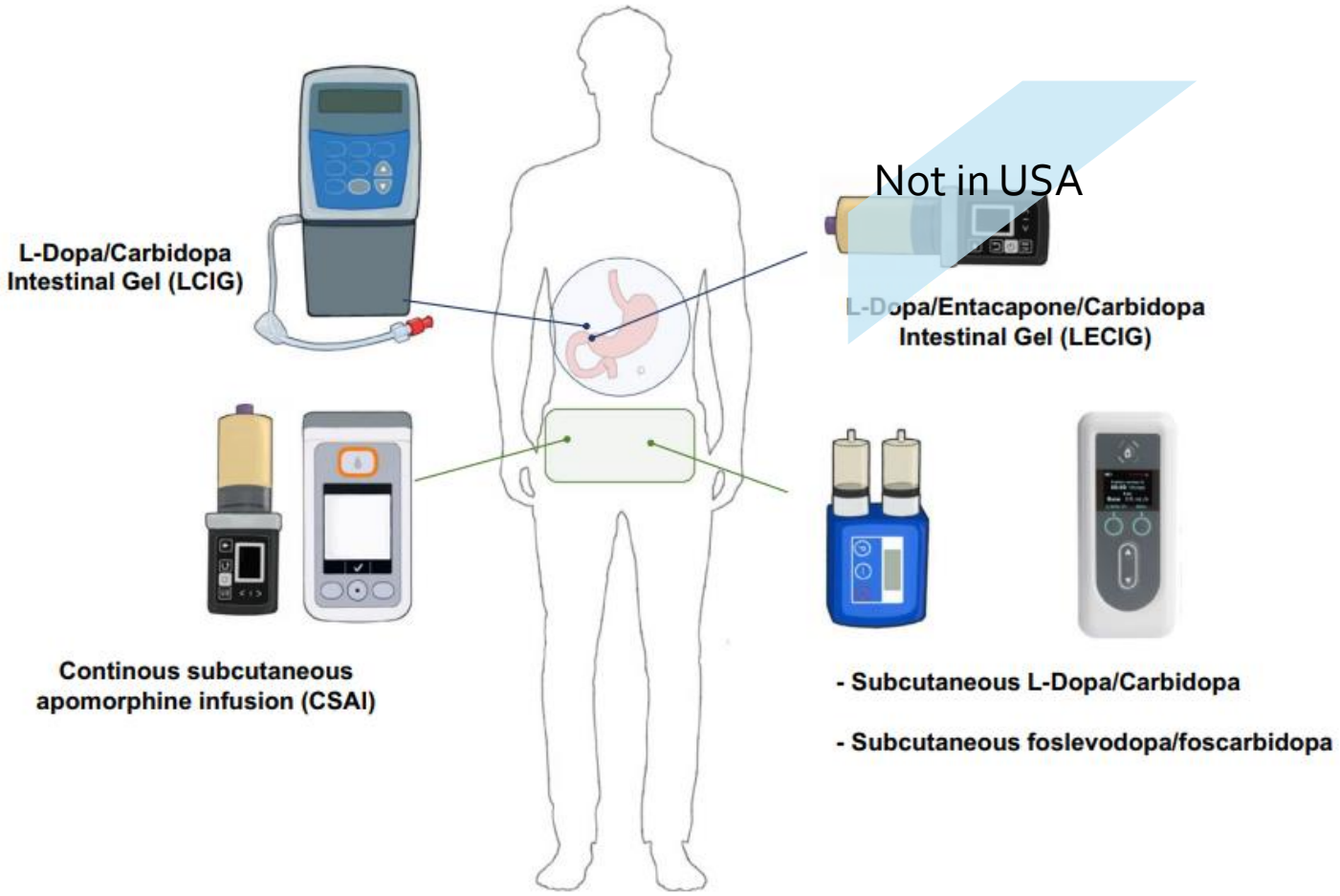
MRI-guided Focused Ultrasound

Reduce OFF time and Dyskinesia
<u>Medication-Resistant Tremor</u>
Improve Quality of Life

Medication tips and resources

- Taking medications on time and avoid missing doses
  - Pillbox, Medication alarms/reminders
- Let doctors know about potential side effects
  -Avoid “prescription cascade” or “snowball effect”
- Choose 1 pharmacy to fill all medications (drug interactions)
- Bring a complete and current medication list to visits
  - Prescription, non-prescription (OTC), supplements, & vitamins
  - Maintain list as it changes, keep one with you

- “Aware and Care kit”, Now the **Hospital Safety Guide** from Parkinson’s Foundation
- https://www.parkinson.org/sites/default/files/documents/Hospital-Safety-Guide.pdf



Antonini A. et al. J Neural Transmission (2023)

Therapies on the Horizon: **Symptomatic**

Under-the-Skin Pumps

Levodopa Based:

- ND0612 – Neuroderm : carbidopa-levodopa
- ABBV-951 – AbbVie: Foscarbidopa-Foslevodopa

Apomorphine:

- SPN-830 – Supernus: Apomorphine

Therapies on the Horizon: **Symptomatic**

- **Tavapadon – "Dopamine mimic" oral daily pill**
  - D1/D5 Selective Dopamine receptor partial Agonist
  - Full results phase III expected Last half of 2024

- **IPX203** (Amneal) – **Carbidopa/Levodopa IR/ER capsule**
  - Lasting 0.9 hr longer than Rytary
  - Likely 3-4x/day dosing
  - FDA approval pending, ? Second half 2024

- **CVN424- Oral pill**: Once daily in early untreated PD
  - Blocks G-protein GPR6 in striatum of brain
  - Non-dopamine, decreases indirect pathway; "Removing the break"
  - Full Results phase III end 2024/2025

Therapies on the Horizon: **Symptomatic**

- **P2B001- Combination Pill**: Rasagiline 0.75mg AND Pramipexole 0.6mg ER
  - once daily in early-stage PD
  - vs. higher doses of Pramipexole (mean equivalent dose of efficacy to 3.2mg/day ER)
  - Less sleepiness, orthostasis

Therapies on the Horizon: **Disease Modifying Therapy**

- **Buntanetap (Annovis; ANVS40) oral daily pill**
  - Block DNA translation of protein TDP-43 (TAR DNA Binding Protein 43 in the brain)
  - Build up of TDP-43 in brain thought to be signal vs. causal in several Neurodegenerative diseases
  - **Positive III data announced July '24, improvement in Non-motor scores w/ 20mg dose**
  - Still in phase 3 trial for PD and AD

- **BIIB122 (Biogen; aka DNL151) oral tablets**
  - Lysosomes are "garbage truck" of the cell
  - Leucine-rich repeat kinase 2 (*LRRK2*)
  - selective, central nervous system-penetrant small molecule inhibitor of LRRK2 that is hypothesized to improve lysosomal dysfunction.
  - **LUMA study- Phase 2b** without LRRK2 mutation and with mutation (prior LIGHTHOUSE study)

Questions?

RESOURCES

Parkinson's Foundation:

- www.Parkinson.org

Michael J Fox Foundation:

- www.MichaelJFox.org

Medication Tools and Drug information:

- www.epill.com
- dailymed.nlm.nih.gov/dailymed/

Parkinson's Consults

www.peakneurocos.com/pd.html

Peak Neurology

Thank you!

Q&A

Why do some drugs work well for some people and not at all for others?

- Parkinsonism vs. Parkinson disease, not everyone a responder
  - Important to know if reached high enough dose to be effective
- Genetic differences
- Drug-Drug interactions
- Disease state interactions affecting absorption and metabolism
- Medication adherence and timing

Should we talk to a pharmacist before taking a new drug? **YES!**

- Dispensing Pharmacists are requiring to offer counseling for new therapy, Do Not refuse it!
- Clinical pharmacist vs. pharmacist
- Can educate on drug-interactions, food-interactions, timing
- Keep up to date med (Rx and OTC) and supplement list, bring to all doctor and healthcare provider visits
- Use 1 pharmacy for all drugs if able

Q&A

Do most doctors know how new drugs work that they prescribe? **I Hope so!**

- If more experienced in that condition, likely to know more
- Do your homework, ask questions – Drug information: https://dailymed.nlm.nih.gov/dailymed/
- Good to have a team approach

Why are drugs so expensive?

- **Pharmacy Benefit Managers (PBMs) – black box to costs between Pharma and Insurance**
- To a lesser degree, Pharma: Expensive for Drug Development and Marketing

Why are time release drugs more expensive?

If they are still Brand (in patent) there is no competition from generic version

Technology for the time release may be more expensive to manufacture

Q&A

Why not drink coffee/caffeine too late into the day?

- Large variability in duration for caffeine use, drugs, smoking, medical conditions (ex. Liver disease, Pregnancy)
- Half-life of drug break down can span 1.5-6 hrs for most people
- **Avoid caffeinated beverages at least 9-12 hours before bedtime**

Q&A

Which drugs affect sleep?

This could be a presentation in itself to answer this, but in short:

Parkinson's Drugs for movement:

-Levodopa and many dopamine agonists (boosters) more likely to increase sleepiness in higher doses

-Selegiline is stimulating, so is dosed twice a day (morning and noontime)

-Drugs that can have side effects of drowsiness, somnolence

-Drugs that are stimulants

-Drugs and Fatigue → NEXT SLIDE

Fatigue: Medications*

Parkinson

- Dopamine agonists
  - Apomorphine
  - Pramipexole
  - Ropinirole
  - Rotigotine
- Levodopa
- Amantadine

Mood & Sleep

- Anxiety (ex. 'Benzos')
- Antidepressants
- Antipsychotics
- Mood stabilizers
- Sleep

Other

- Allergy
- Heart & blood pressure
- Pain (ex. opioids)
- Muscle relaxants
- Urinary incontinence
- Seizure
- Cancer chemotherapy

*= Not all-inclusive list