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Information provided in this talk is only intended as general information and not as specific medical advice or advertisement for a specific product.

For specific questions about your diagnosis or treatments that are right for you, please speak with your personal care team.

OVERVIEW

- What is Parkinson's Disease?
- Role of Exercise
- Goals of Medication Treatment and When to Start
- Current Medications for Parkinson's Disease
- Advanced Therapies
- Clinical Trials

PARKINSON'S DISEASE (PD) BY NUMBERS

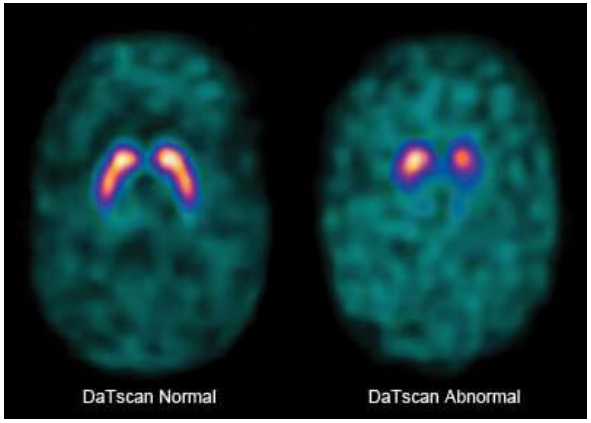
- **2nd** Most common neurodegenerative disorder (after Alzheimer's)
- **90,000** people diagnosed in US per year with PD
- **$52 billion** annual spending

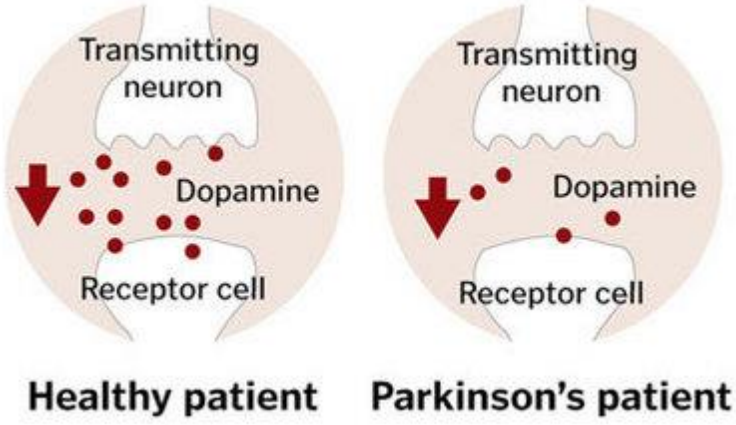
WHAT IS PARKINSON'S DISEASE (PD)?

Parkinson disease is a **Neurodegenerative disease** that impacts **body movements**, but can also affect thinking, mood, sleep, and other body functions.

DOPAMINE DYSFUNCTION IN PD

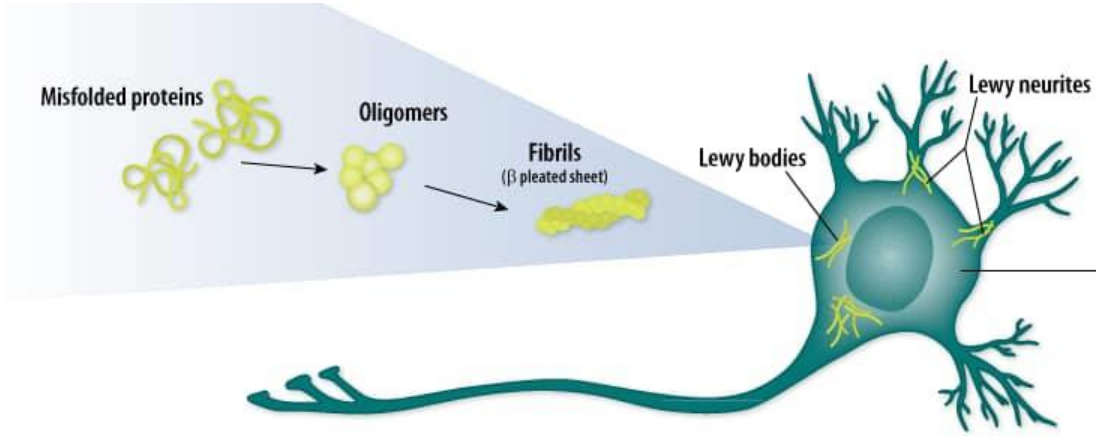
- **Dopamine-producing** brain cells, or neurons, are especially impacted in PD
- **Dopamine** is a **messenger molecule** (neurotransmitter) in the brain that **helps nerve cells communicate** and coordinate important functions such as smooth controlled movements, motivation and reward, learning, attention, …





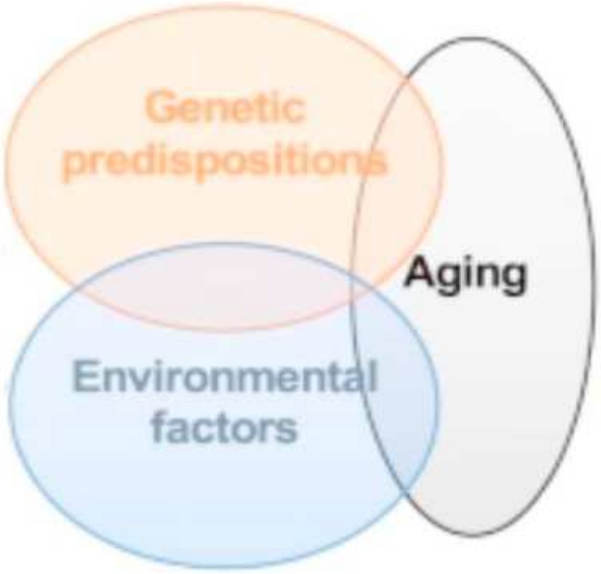
PD IS MORE THAN A DOPAMINE PROBLEM

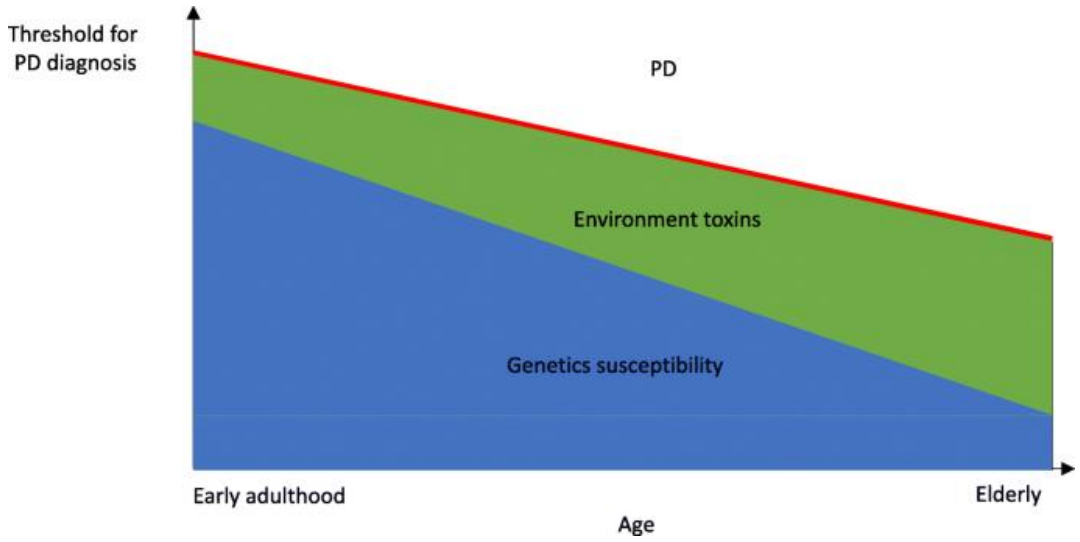
- But Parkinson's is **more than just a dopamine problem.** Other brain systems are affected too!
- Abnormal clumps of a protein called **alpha-synuclein** often build up inside brain cells. These clumps, known as **Lewy bodies**, are considered an important feature of the disease.



THE EXACT CAUSE REMAINS UNKNOWN

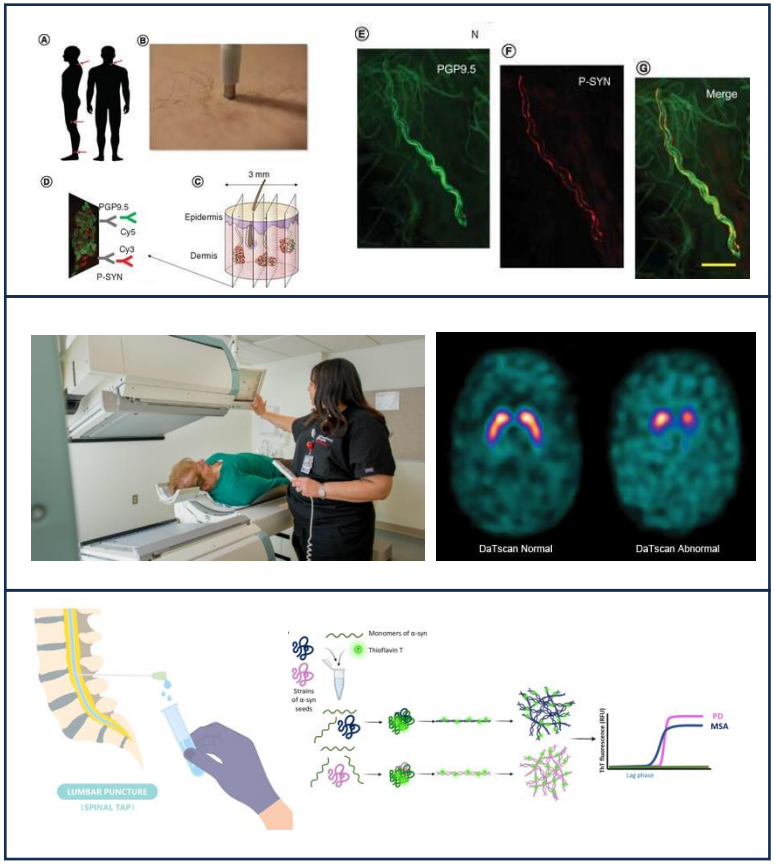
Likely a mixed disease involving a "multiple-hit" process





PARKINSON'S DISEASE (PD) IS A CLINICAL DIAGNOSIS

- Based on:
  - presence of the typical motor +/- non-motor symptoms
  - Absence of Red Flags
  - Response to Levodopa
- No single test can prove or rule our Parkinson disease
  - Biomarkers – skin biopsy or CSF-basec synuclein tests, DATscan



PARKINSON'S DISEASE (PD) MOTOR SYMPTOMS

Slowed movements (bradykinesia)

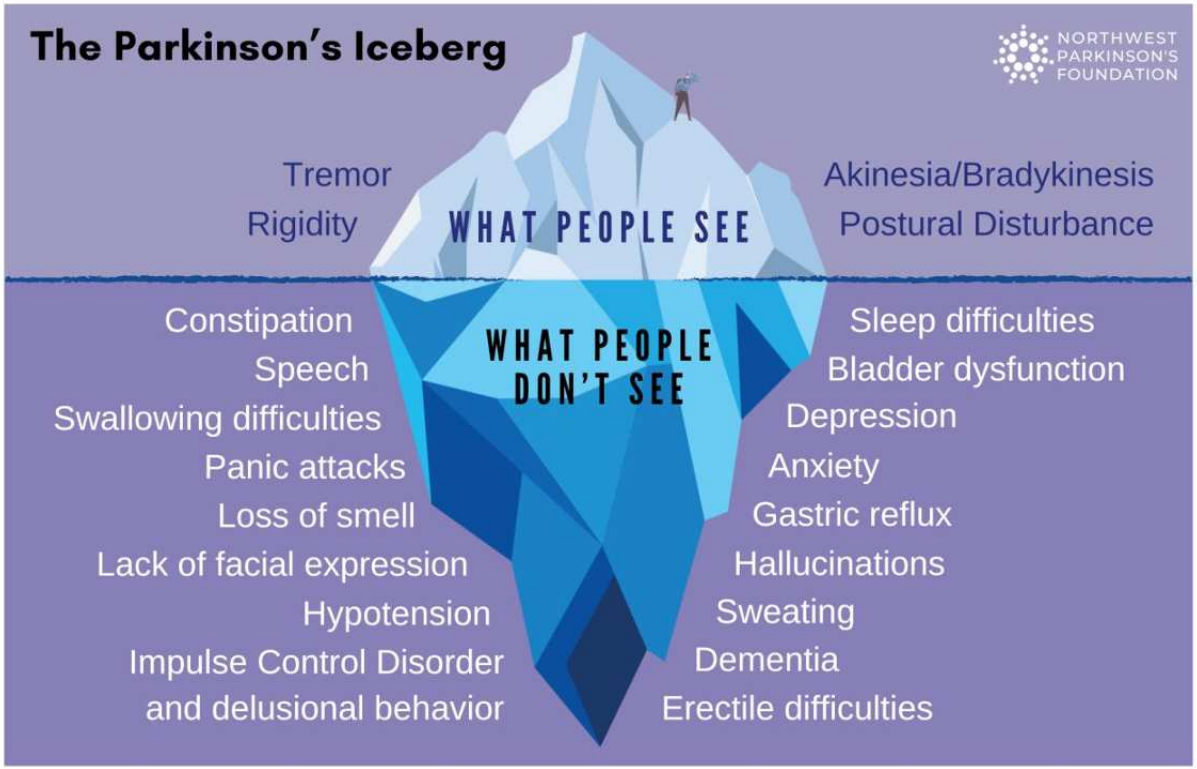
+

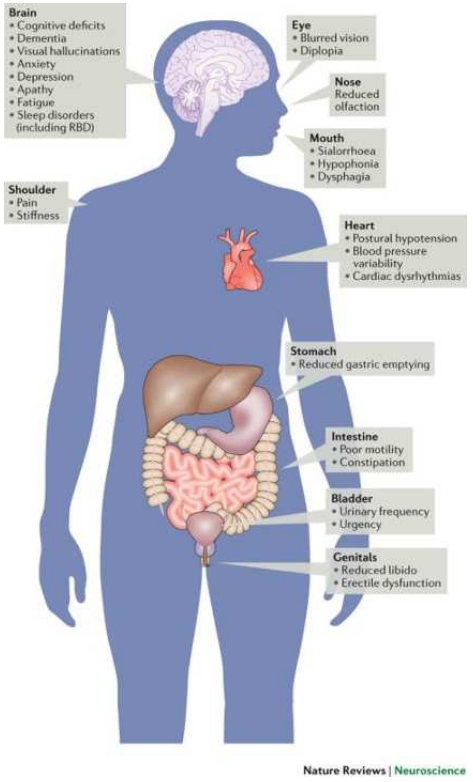
At least one of the following:

- +/- Muscle stiffness (rigidity)
- +/- rest tremor
- +/- balance difficulties (postural instability)

PARKINSON DISEASE IS A MULTI-SYSTEMIC DISORDER

Not everyone will experience every symptom



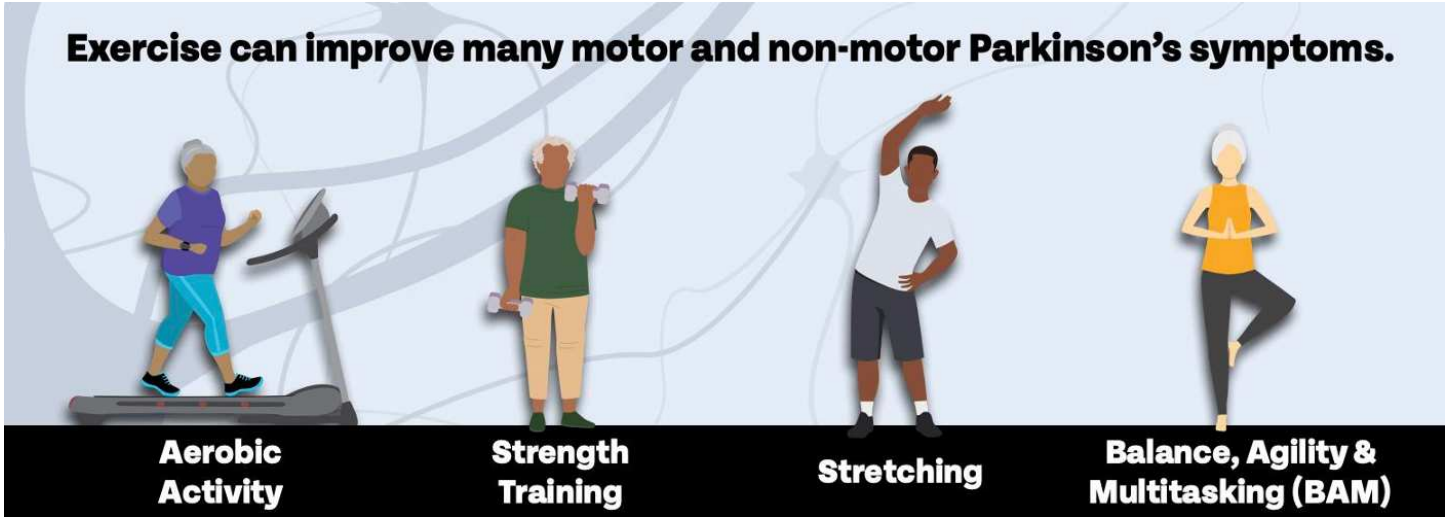


IMPORTANCE OF EXERCISE IN PARKINSON DISEASE

- As of now, there is no cure or disease modifying treatment for Parkinson disease
- However, regular exercise can improve symptoms and slow down the progression of PD

TIPS FOR EXERCISE IN PD

- Safety 1st – choose exercises you can do safely, exercise in ON state and in safe environments
- Aim for 150 min per week of moderate aerobic activity.
- Consistency is Key!
- Build up slowly if not already engaging in regular exercise
- Consider seeing a Physical therapist familiar with PD



HTTPS://STANFORDHEALTHCARE.ORG/FOR-PATIENTS-VISITORS/NEUROSCIENCE-SUPPORTIVE-CARE-PROGRAM.HTML

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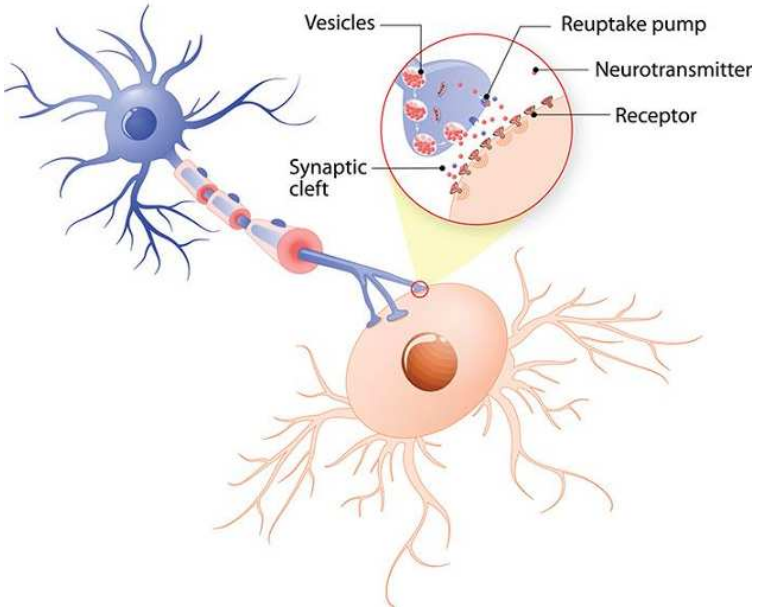
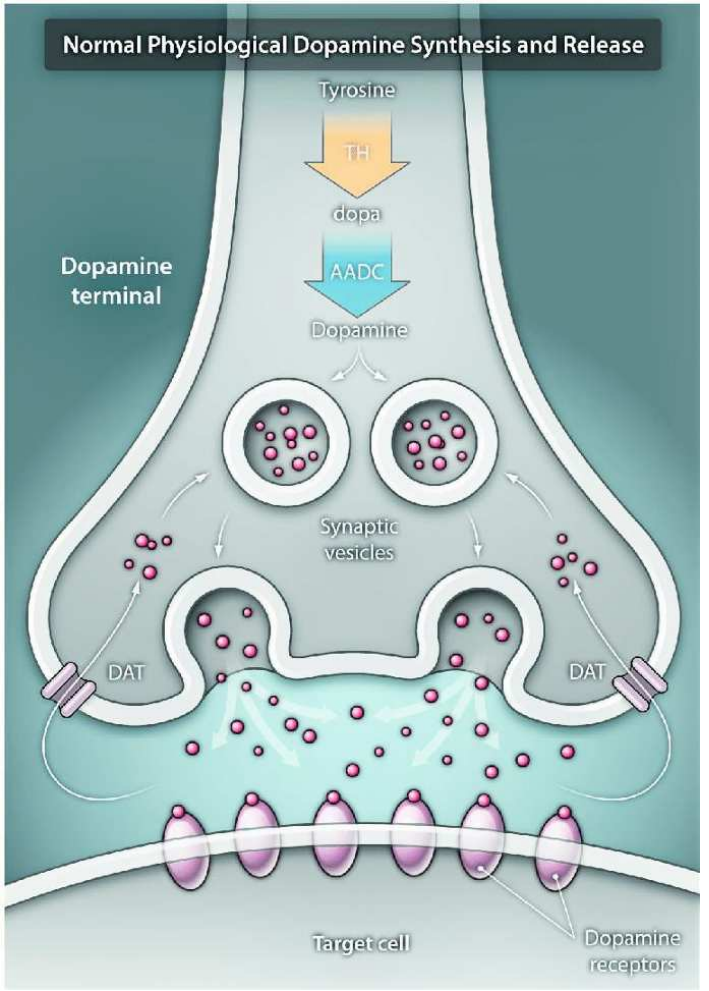
GOALS OF THERAPY

- While there are no cures or disease-slowing medications, there are many medications that can help **decrease motor (and some non-motor) symptoms** and **IMPROVE QUALITY OF LIFE**
- Start medications when quality of life is affected.

Brief review of PD medications

MEDICATIONS USED TO HELP THE MOTOR SYMPTOMS PRIMARILY TARGET DOPAMINE

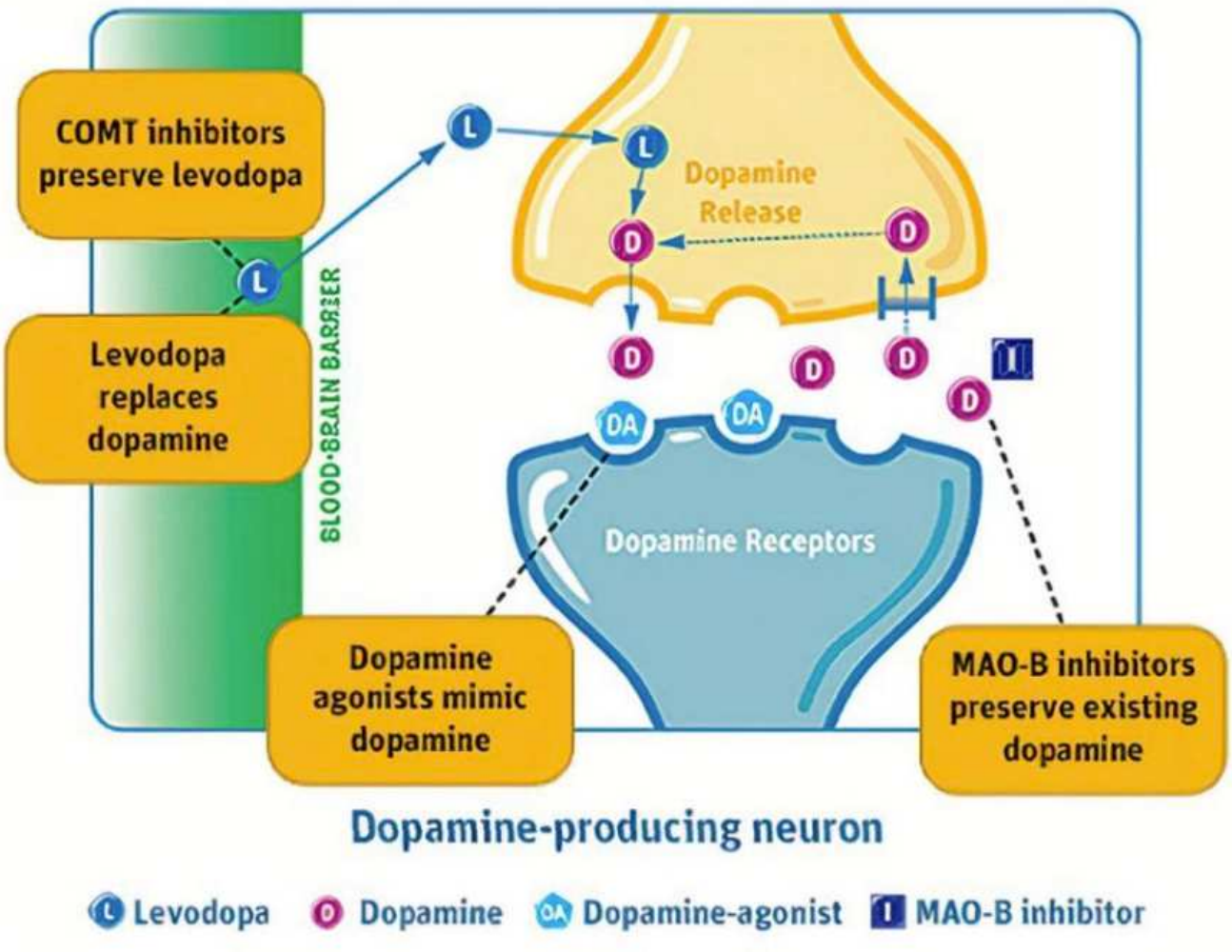




There are many Dopaminergic medications with different formulations

Class	Drug (brand examples)	Formulations / routes
Levodopa therapies & combos	Carbidopa/levodopa (Sinemet)	Oral IR tablets; Oral CR/ER tablets
	Carbidopa/levodopa ER (Rytary)	Oral extended-release capsules
	Carbidopa/levodopa ER (Crexont, IPX203)	Oral extended-release capsules
	Carbidopa/levodopa functionally scored (Dhivy)	Oral scored tablets
	Levodopa (Inbrija)	Inhalation powder capsules via inhaler
	Carbidopa/levodopa intestinal gel (Duopa)	Enteral suspension via PEG-J (16-hr pump infusion)
	Foscarbidopa/foslevodopa (Vyalev)	24-hr continuous subcutaneous infusion (pump)
	Carbidopa/levodopa/entacapone (Stalevo)	Oral tablets
Dopamine agonists	Pramipexole (Mirapex)	Oral tablets (IR & ER)
	Ropinirole (Requip)	Oral tablets (IR & ER)
	Rotigotine (Neupro)	Transdermal patch (24-hr)
	Apomorphine (Apokyn)	Subcutaneous injection (pen cartridges)
MAO-B inhibitors	Selegiline (Eldepryl, Zelapar ODT)	Oral tablets/capsules; Orally disintegrating tablets
	Rasagiline (Azilect)	Oral tablets
	Safinamide (Xadago)	Oral tablets
COMT inhibitors	Entacapone (Comtan, generics)	Oral tablets
	Opicapone (Ongentys)	Oral capsules
Adenosine A2A antagonist	Istradefylline (Nourianz)	Oral tablets
Amantadine	Amantadine IR (Symmetrel)	Oral capsules, tablets, syrup/solution
	Amantadine ER (Gocovri)	Oral extended-release capsules
	Amantadine ER (Osmolex ER)	Oral extended-release tablets

CLASSES OF DOPAMINERGIC MEDICATIONS



LEVODOPA IS THE GOLD STANDARD, MOST EFFECTIVE MEDICATION FOR MANAGING PD MOTOR SYMPTOMS

- 1911: Synthetic L-Dopa 1st produced
- 1913: L-Dopa also isolated from Fava bean seedlings
- 1960: Dopamine deficiency identified in brains of patients with PD
- 1961: 1st administration of L-Dopa to PD patients
- 1970: FDA approval of L-Dopa for PD in the US
- Early 1970s: Carbidopa added to L-Dopa to decrease nausea (the most common early side effect)

LEVODOPA – MANY FORMULATIONS

Levodopa Formulations

- Carbidopa-Levodopa/Sinemet®
  - Immediate Release (IR)
  - Controlled Release (CR)
- Rytary ® Crexont ®
- Duopa® Vyalev®
- Inbrija ®

Benefits:

- reduce tremor and rigidity
- improve speed of movement
- May also improve energy, thinking, or balance.

All formulations must be taken at various times daily to be effective, but some are longer-acting (Sinemet CR®, Rytary®, Crexont ®)

LEVODOPA FACTS AND FICTION

- Myth: Levodopa speeds up Parkinson's disease.
- Myth: You should postpone starting Levodopa as long as possible.
- Myth: Levodopa will only work for 5 years.

NO CONVINCING EVIDENCE THAT LEVODOPA HARMS PATIENTS OR SLOWS DISEASE PROGRESSION

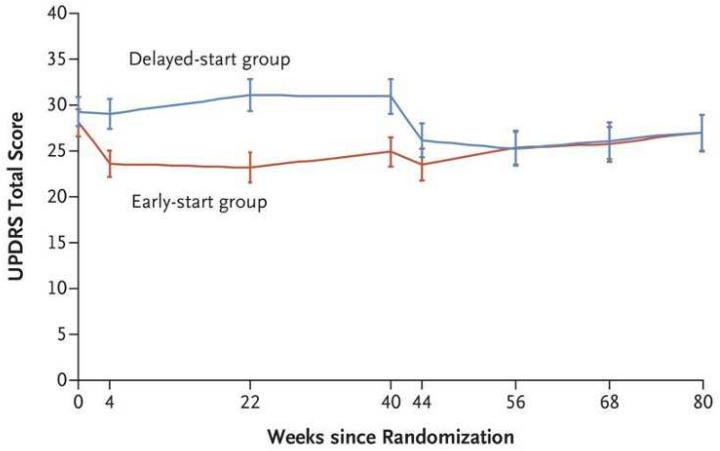
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

Authors: Constant V.M. Verschuur, M.D., Sven R. Suwijn, M.D., Judith A. Boel, Ph.D., Bart Post, M.D., Ph.D., Bas R. Bloem, M.D., Ph.D., Johannes J. van Hilten, M.D., Ph.D., Teus van Laar, M.D., Ph.D., +7, for the LEAP Study Group* Author Info & Affiliations

Published January 23, 2019 | **N Engl J Med 2019;380:315-324** | **DOI: 10.1056/NEJMoa1809983** | **VOL. 380 NO. 4**



Movement Disorders
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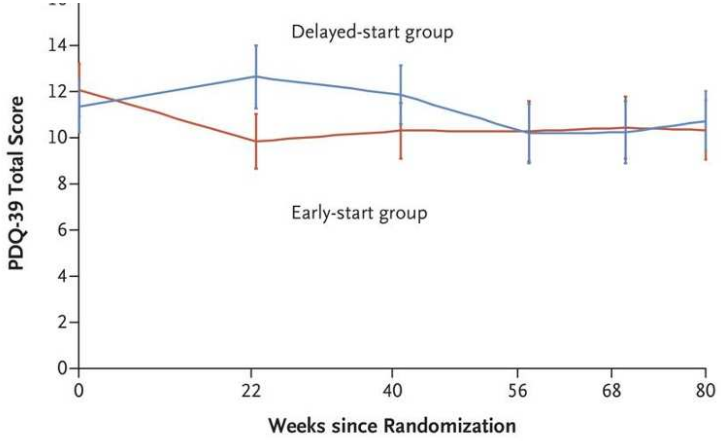
RESEARCH ARTICLE | Open Access

Long-Term Follow-Up of the LEAP Study: Early Versus Delayed Levodopa in Early Parkinson's Disease

Henrieke L. Frequin MD, Constant V.M. Verschuur MD, Sven R. Suwijn MD, PhD, Judith A. Boel PhD, Bart Post MD, PhD, Bastiaan R. Bloem MD, PhD, Johannes J. van Hilten MD, PhD ... See all authors

First published: 21 April 2024 | https://doi.org/10.1002/mds.29796 | VIEW METRICS



RELATIONSHIP BETWEEN LEVODOPA AND DYSKINESIAS

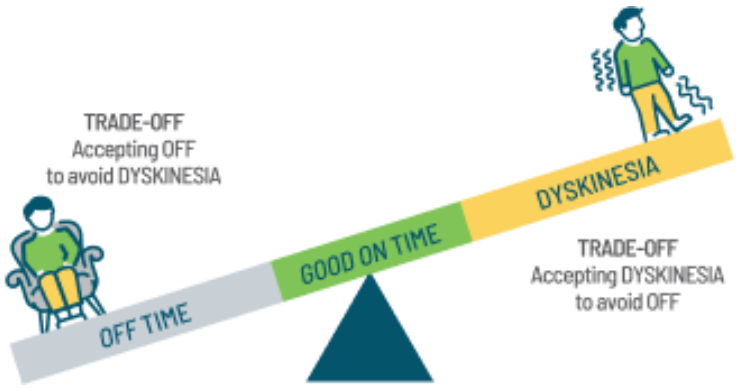
- **Dyskinesias** - involuntary, writhing, dance-like or jerky movements of the body that can emerge when some patients with PD have been taking Levodopa for a while
  - It's not simply a result of total Levodopa exposure
  - disease duration/severity and individual patient susceptibility factors also matter (buffering ability of the brain)

If 2 identical patients develop PD at the same time:

- Patient A starts levodopa at diagnosis.

- Patient B delays levodopa for 2 years despite symptomatic disability.

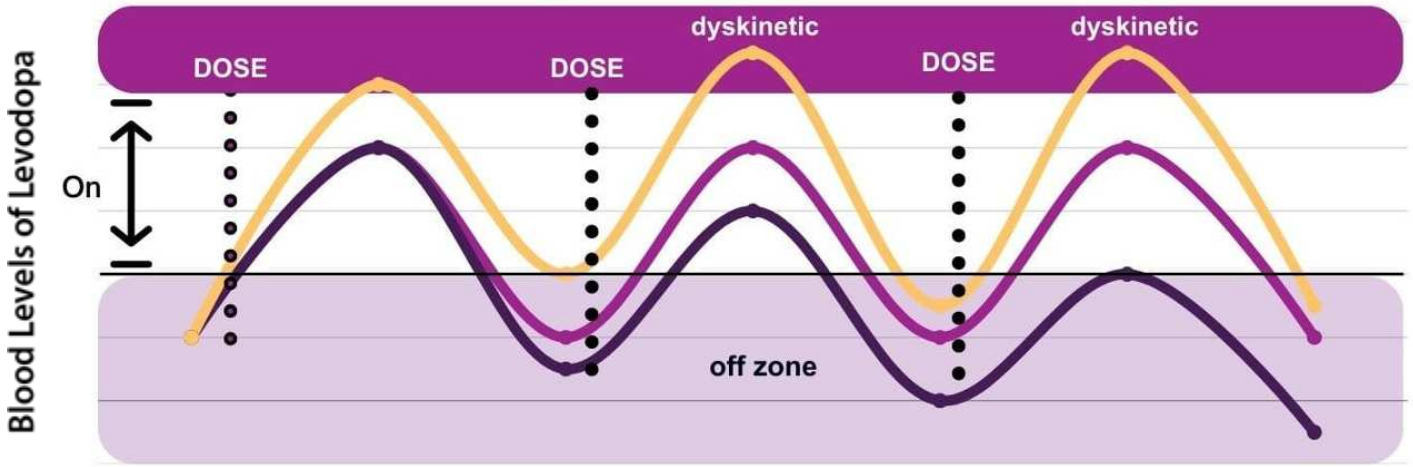
=> Patient B will **not gain a major reduction in lifetime dyskinesia risk**, but will spend 2 years with worse symptom control and reduced quality of life



RULES OF THUMB FOR MEDICATION INITIATION

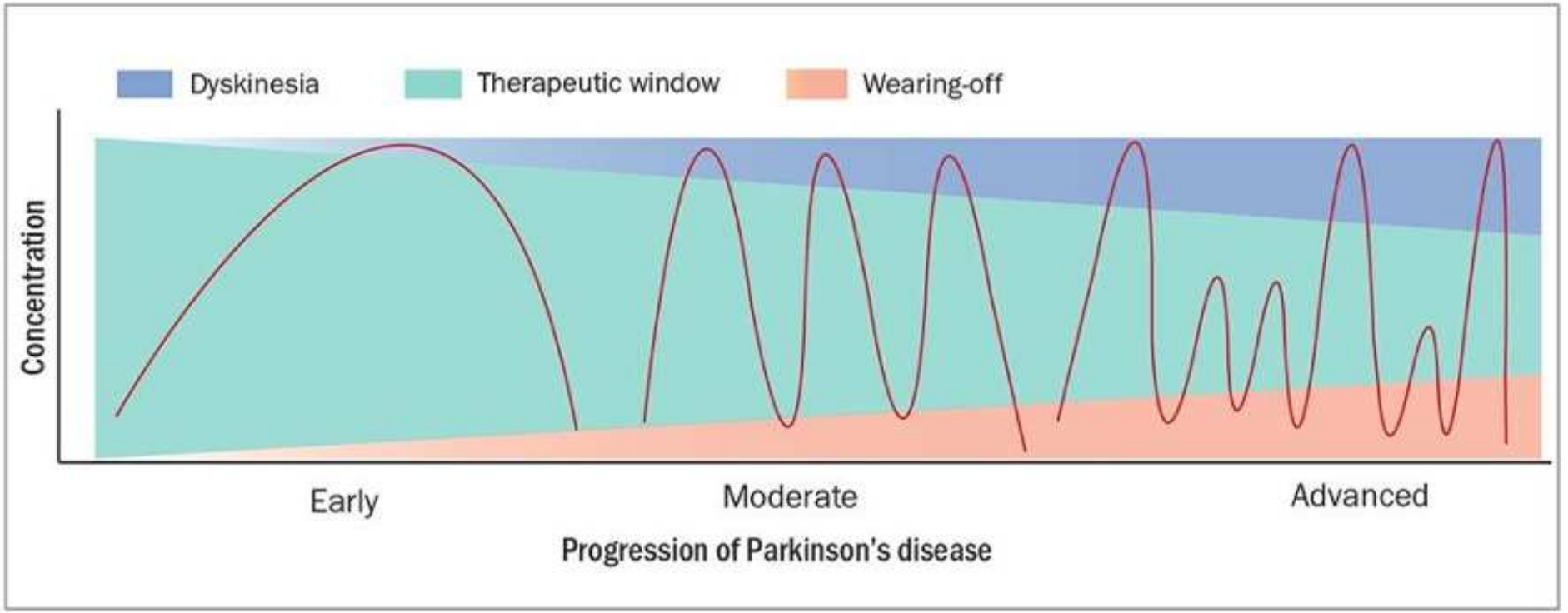
- Start low and increase gradually to **improve tolerance** and **find the minimum effective dose**
- Over time, as the disease progresses and makes less of its own dopamine, the medication doses need to be increased to maintain motor functioning

DOSE AND TIMING OF LEVODOPA INTAKE MATTER!



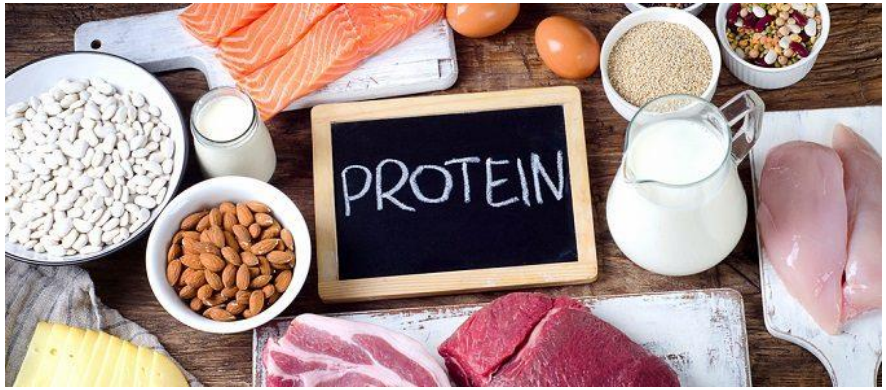
Delayed or missed doses can lead to breakthrough in symptoms

MEDICATION REGIMEN AND BALANCE OF ON AND OFF TIMES CAN CHANGE AS THE DISEASE PROGRESSES



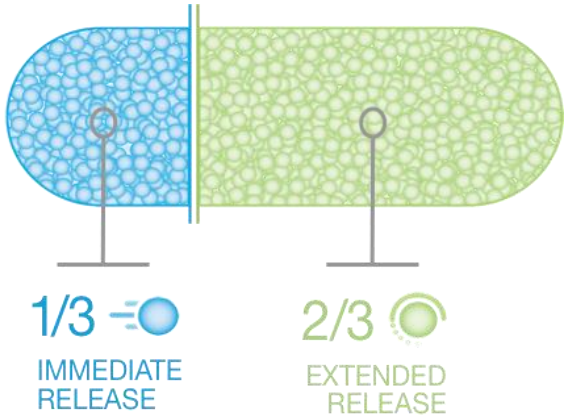
INTERACTION WITH PROTEIN

- Levodopa is absorbed into the brain usually in 20-40 min.
- Protein, taken at the same time, may interfere with levodopa absorption.
- Ideally, Levodopa should be taken 30min before or 1 hour after protein-rich meals for maximum absorption.

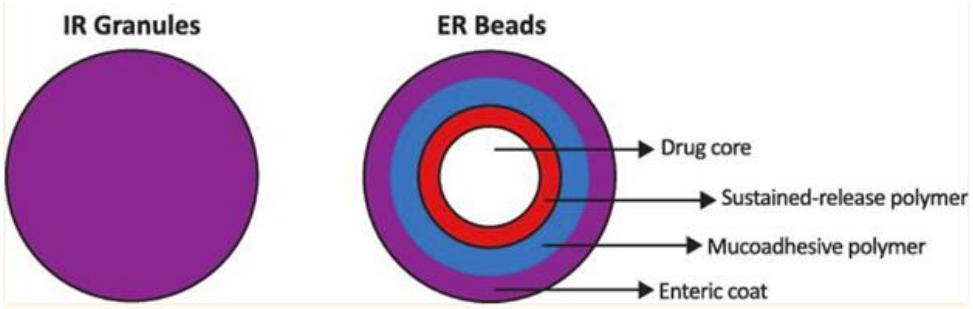


NEWER FORMULATIONS OF LEVODOPA

Rytary



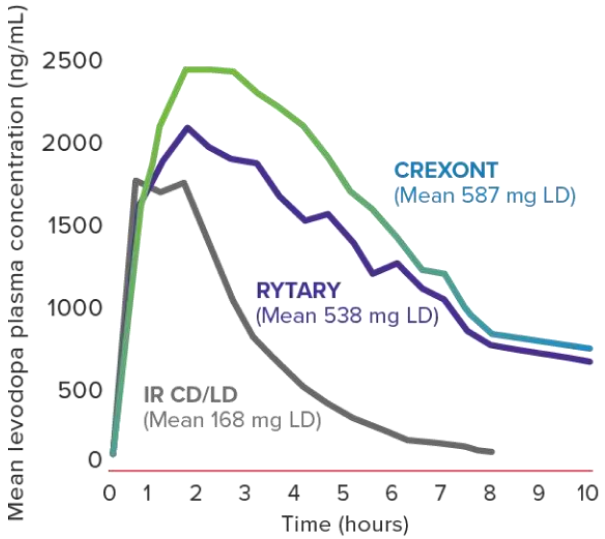
Crexont

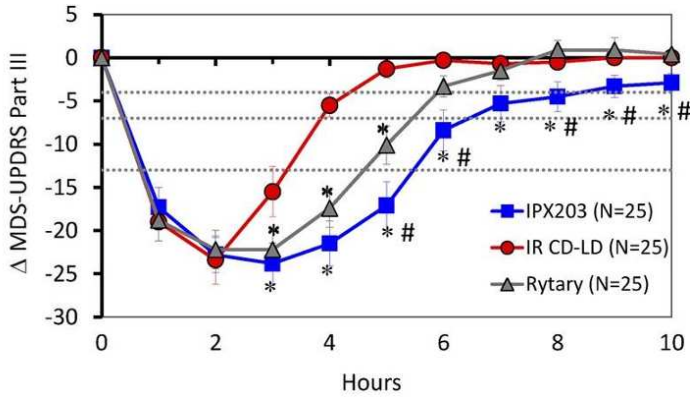


COMPARISON OF SINEMET VS. RYTARY & CREXONT

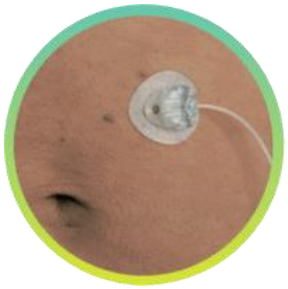
- Analysis of <u>good on-time per dose</u> gathered from separate phase 3 double-blind randomized trials:
  - increase of <u>1.16 hours</u> for Rytary vs. IR CD-LD per dose
  - increase of <u>1.55 hours</u> for Crexont vs. IR CD-LD per dose

~20min longer effect per dose for Crexont vs. Rytary

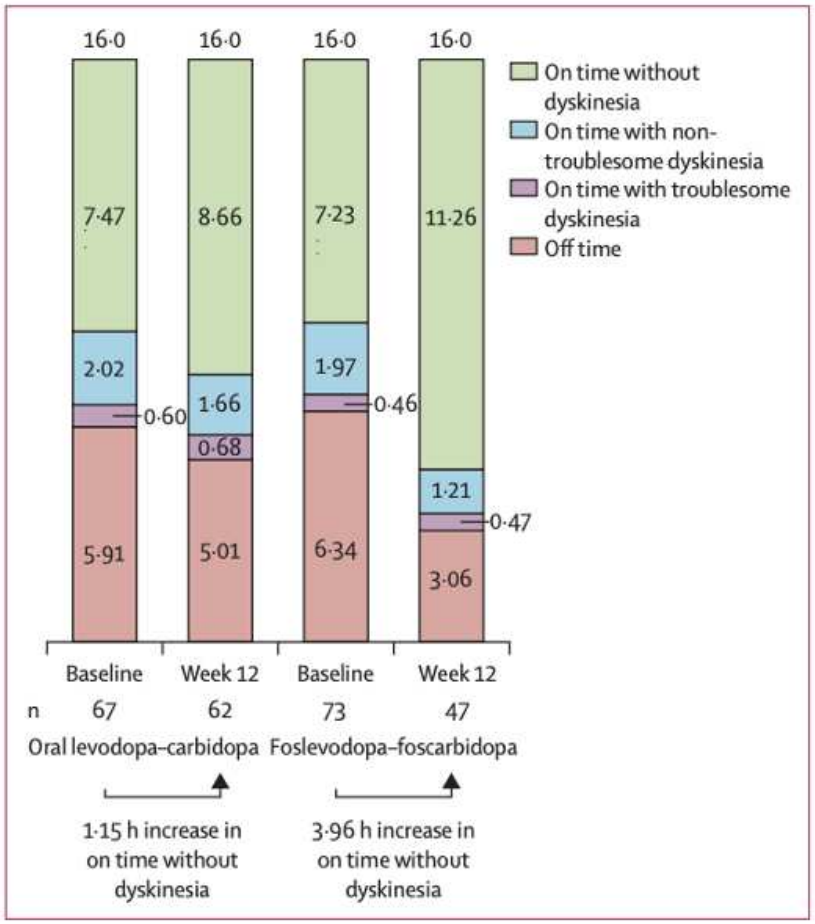




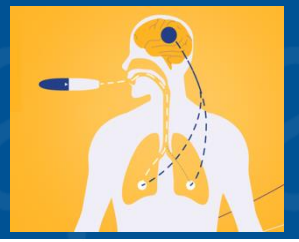
FOSCARBIDOPA/FOSLEVODOPA PUMP (VYALEV)

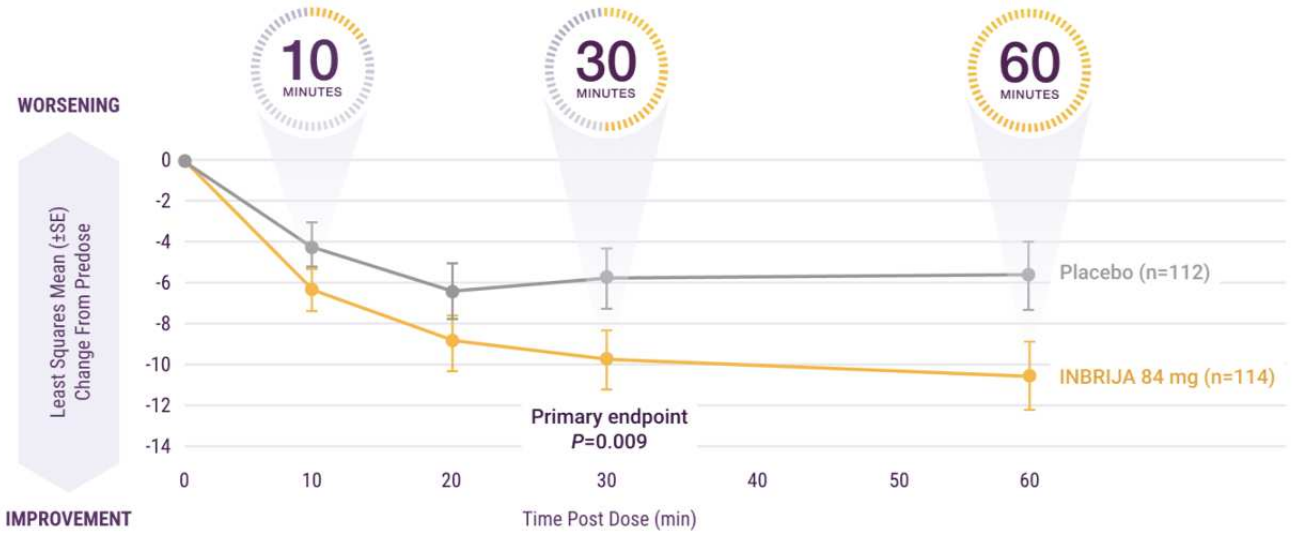


- FDA approved October 2024
- Delivered under the skin
- Continuous, 16 or 24-hour infusion



LEVODOPA INHALATION POWDER (INBRIJA)

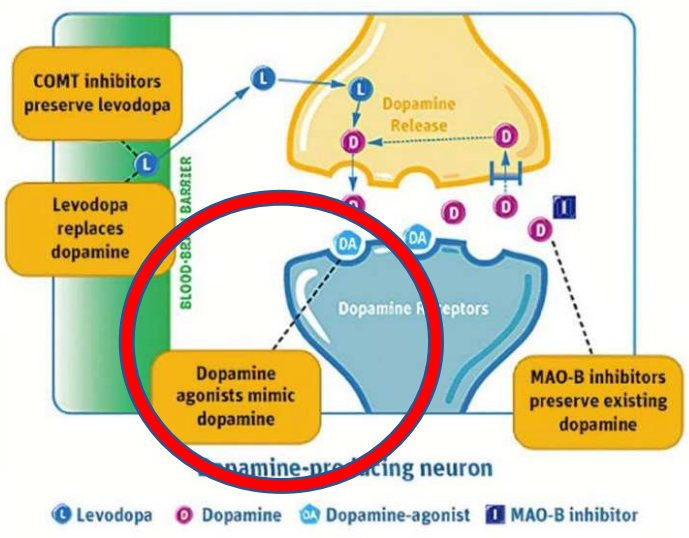




DOPAMINE AGONISTS

Dopamine Agonists

- Pramipexole/Mirapex®
- Ropinirole/Requip®
- Rotigotine/Neupro®
- Apomorphine/Apokyn®



- Act on dopamine receptors directly
- Can be used as first medication in early PD or as an add-on treatment later

PROS AND CONS OF DOPAMINE AGONISTS

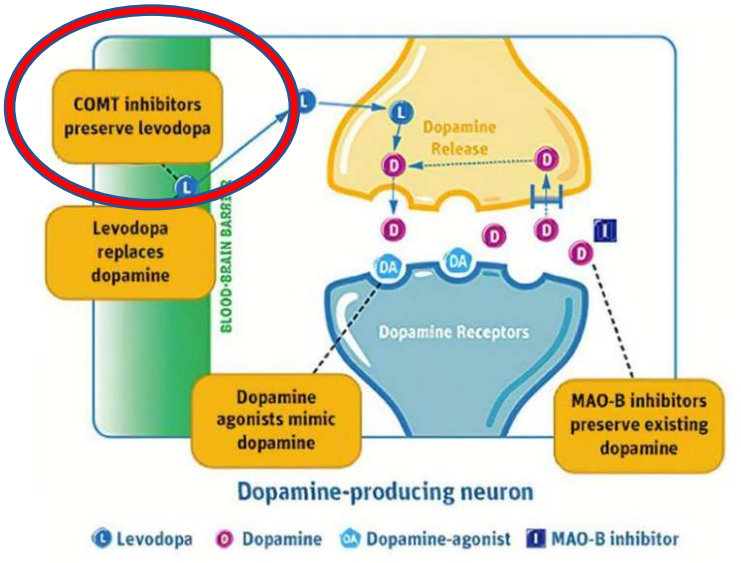
- PROS
  - Can be dosed less frequently or once daily (XL, patch)
  - Less risk of nausea than levodopa
  - Do not compete with protein in food for absorption

- CONS
  - More risk of impulse control disorders (ICD)
    - Gambling, sexual behaviors, eating, compulsions
  - More risk of drowsiness and sleep attacks

COMT INHIBITORS

COMT Inhibitors

- Entacapone/Comtan®
- Opicapone/Ongentys®
- Carbidopa-Levodopa+Entacopone/Stalevo®

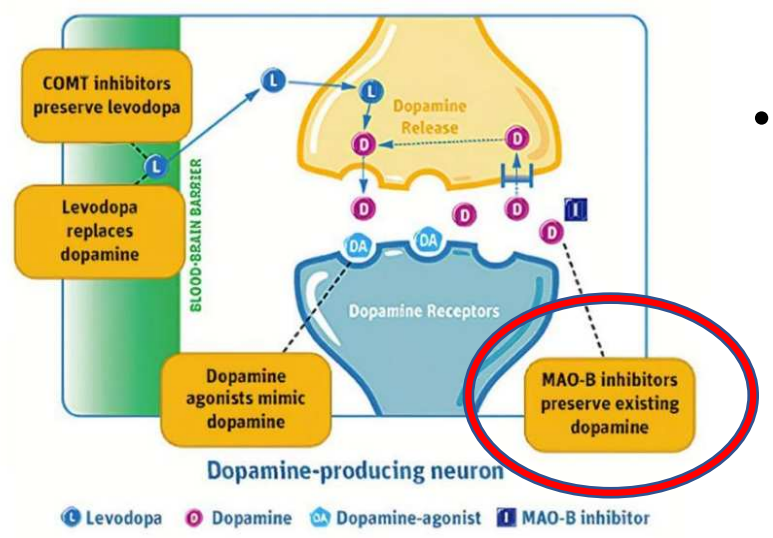


- Decrease breakdown of levodopa
- Act as Levodopa "extender" - Need to be used in combination with levodopa to work
  - Entacapone - dosed with each dose of levodopa
  - Opicapone – dosed daily
- *Side effects*: diarrhea, abdominal pain, discoloration of urine / body fluids

MAO-B INHIBITORS

MAO-B Inhibitor

- Selegiline/Zelapar®/Eldepryl®
- Rasagiline/Azilect ®
- Safinamide/ Xadago ®



- Also decrease breakdown of dopamine
- Dosed once or twice per day
- Can be used as first medication in early PD or as an add-on treatment later
- Fairly mild effect

- *Side effects*: headache, joint ache, nausea, concerns about drug-drug interactions; Selegiline may contribute to insomnia (metabolized to an amphetamine metabolite).

AMANTADINE

- Amantadine/Symmetrel®
- Amantadine ER/Gocovri®
- Amantadine ER/Osmolex ®

- Introduced as an antiviral agent
- Found to be useful in PD in the 1960s
- Improves tremor, slowness, rigidity
- **Only medication that can reduce dyskinesias**

- *Side effects*: dry mouth, Confusion, hallucinations, swelling, constipation

ANTI-CHOLINERGICS – TRIHEXYPHENIDYL (ARTANE)

- Usually dosed 2 or 3 times per day
- May be used for
  - Medication refractory tremor
  - Abnormal postures (dystonia)

- *Side Effects*: dry mouth, blurred vision, constipation, nausea, difficulty emptying the bladder, cognitive slowing, sedation

Which to choose with so many options?

- Few head to head comparisons

npj | Parkinson's Disease

NPJ Parkinsons Dis. 2023 Oct 19;9:143. doi: 10.1038/s41531-023-00589-8

Comparative efficacy and safety of adjunctive drugs to levodopa for fluctuating Parkinson's disease - network meta-analysis

Wataru Sako [1,✉], Yuki Kogo [2], Michinori Koebis [2], Yoshiaki Kita [3], Hajime Yamakage [4], Takayuki Ishida [2], Nobutaka Hattori [1]

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

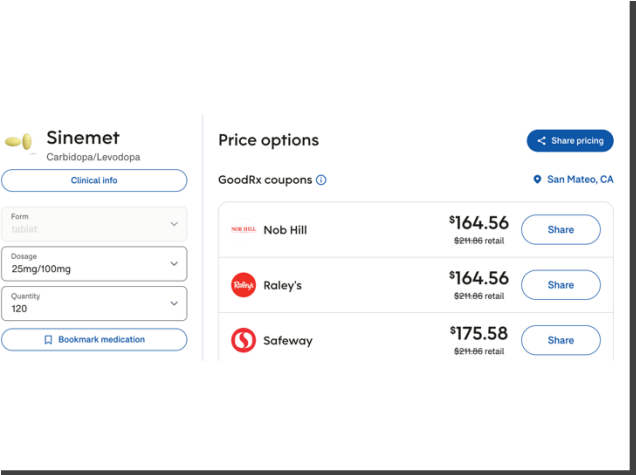
REVIEW | Open Access

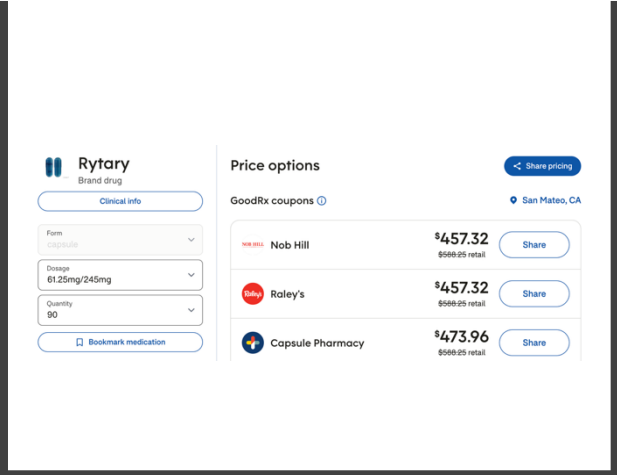
Update on Treatments for Parkinson's Disease Motor Fluctuations – An International Parkinson and Movement Disorder Society Evidence-Based Medicine Review

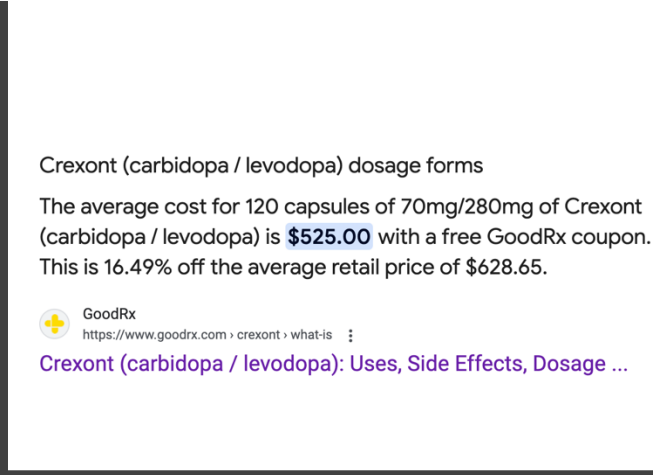
Rob M.A. de Bie MD, PhD, Regina Katzenschlager MD, Bart E.K.S. Swinnen MD, PhD, Marina Peball LLM, PhD, Shen-Yang Lim MD, Tiago A. Mestre MD, PhD ... See all authors

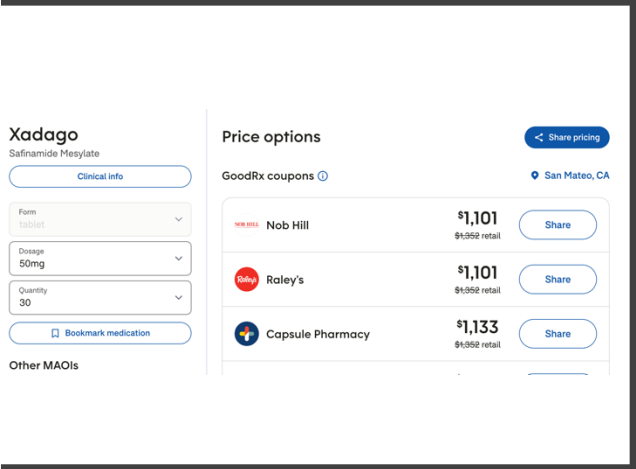
First published: 08 March 2025 | https://doi.org/10.1002/mds.30162

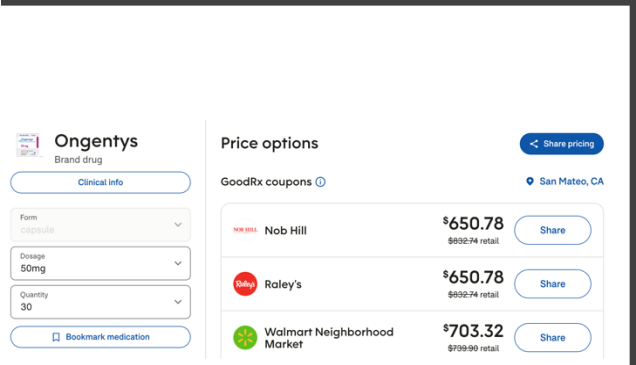
- Levodopa remains the cornerstone of PD therapy
- Talk to your clinician!







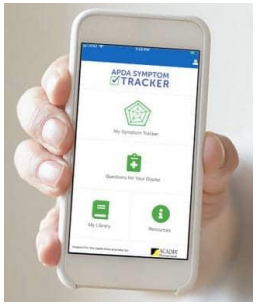




Cost & coverage are important considerations

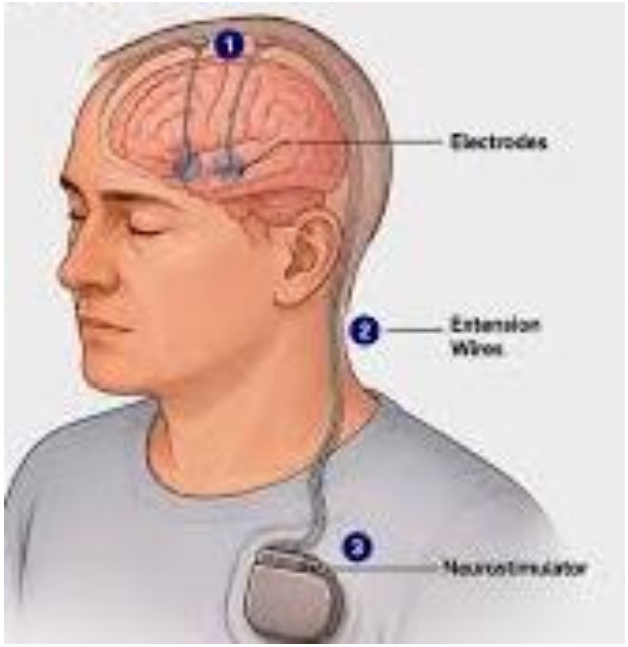
ORGANIZATION OF MEDICATIONS

- Important to keep medications organized.
- Ideally wake up and go to sleep around the same time to help keep the medication times stable.
- Understand the goal and potential side effect for each medicine
- Pay attention to your specific symptoms – not just whether you feel good or bad – to help your clinicians make necessary adjustments to your regimen

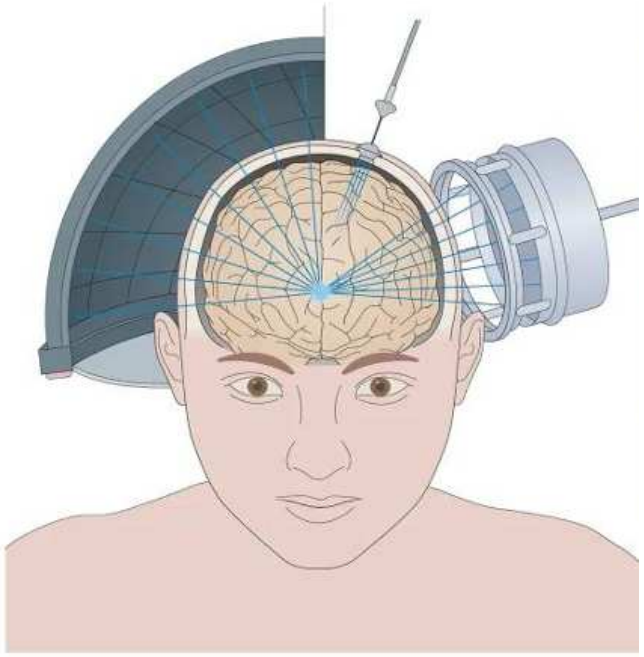


SURGICAL OPTIONS FOR MOTOR FLUCTUATIONS OR MEDICATION REFRACTORY TREMOR

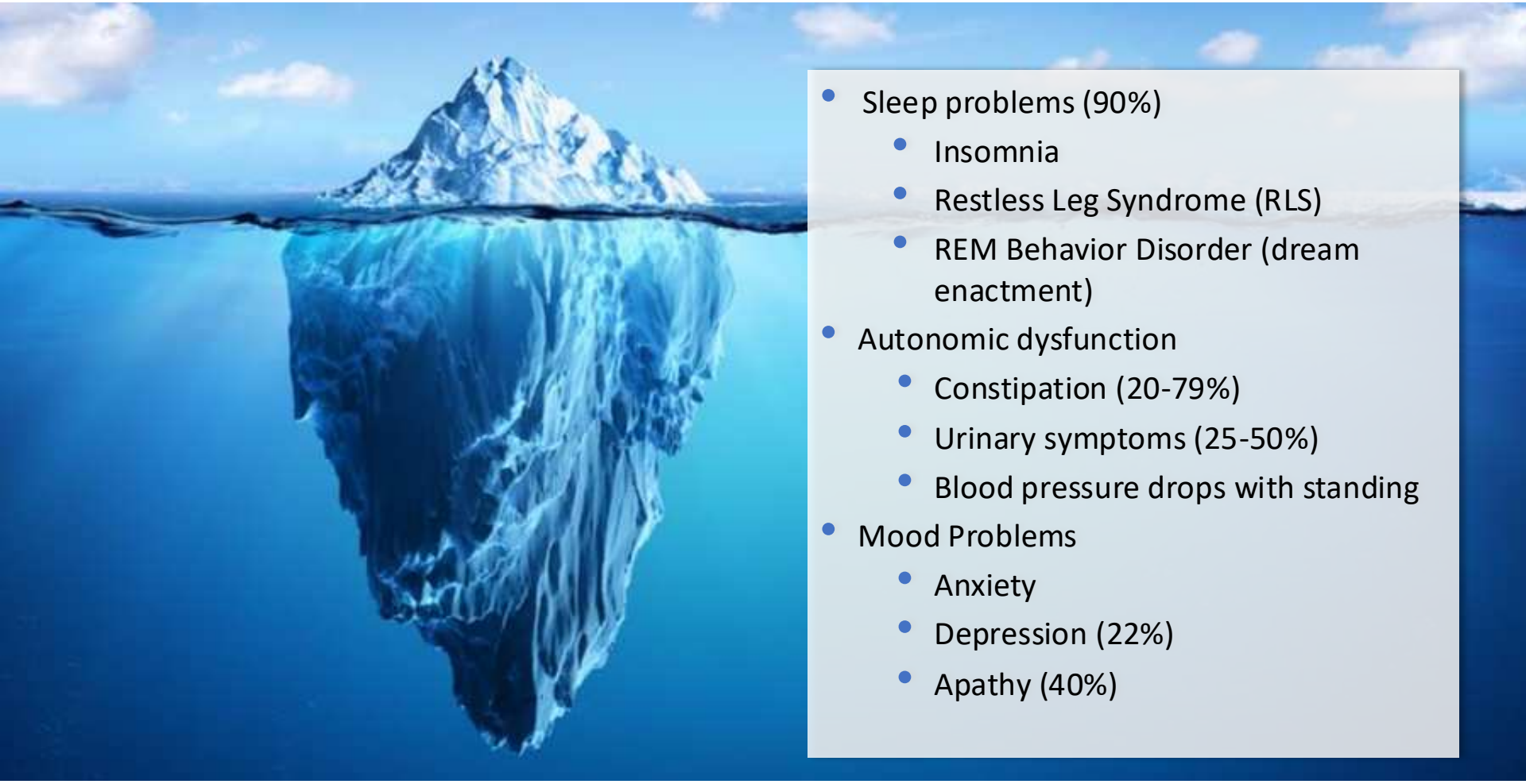
Deep Brain Stimulation (DBS)



Focused Ultrasound (FUS)



THERE ARE ALSO TREATMENTS FOR SOME OF THE NON-MOTOR SYMPTOMS OF PD!



- Sleep problems (90%)
  - Insomnia
  - Restless Leg Syndrome (RLS)
  - REM Behavior Disorder (dream enactment)
- Autonomic dysfunction
  - Constipation (20-79%)
  - Urinary symptoms (25-50%)
  - Blood pressure drops with standing
- Mood Problems
  - Anxiety
  - Depression (22%)
  - Apathy (40%)

CLINICAL TRIALS

apda AMERICAN PARKINSON DISEASE ASSOCIATION

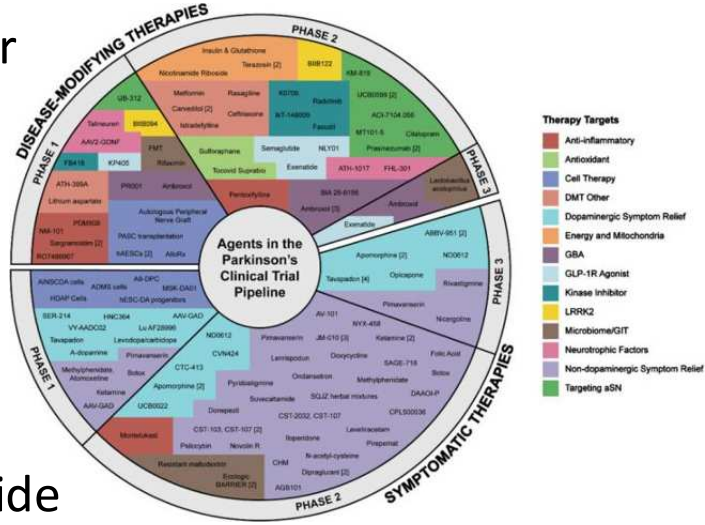
Strength in optimism. Hope in progress.

WHAT ARE CLINICAL TRIALS?

- Studies on human participants designed to answer specific questions.

- Observational vs Interventional

- <u>Importance of Trials:</u>
  - The number of people with PD is projected to double by 2030 to **9.5 million people** worldwide
  - Better understanding of PD and better treatments are needed!
  - 30% of trials don't recruit anyone; 85% finish late
  - Less than 1% of those with PD participate in clinical trials
  - ~70% of PD pts are unaware of trials



PD GENERATION STUDY – OBSERVATIONAL GENETIC REGISTRY STUDY

PD GENERation is a research study that provides genetic testing and genetic counseling at no cost for people diagnosed with Parkinson's disease

What's in it For You?

- Learn about your family's risk for Parkinson's.
- Access to genetic counseling at no cost.
- Connections to clinical trials relevant to your results.

What's in it for the PD Community?

- Researchers will better understand the genetic factors that contribute to PD.
- Accelerated progress toward new treatments.
- Diversified Parkinson's research.

Parkinson.org/PDGENEration

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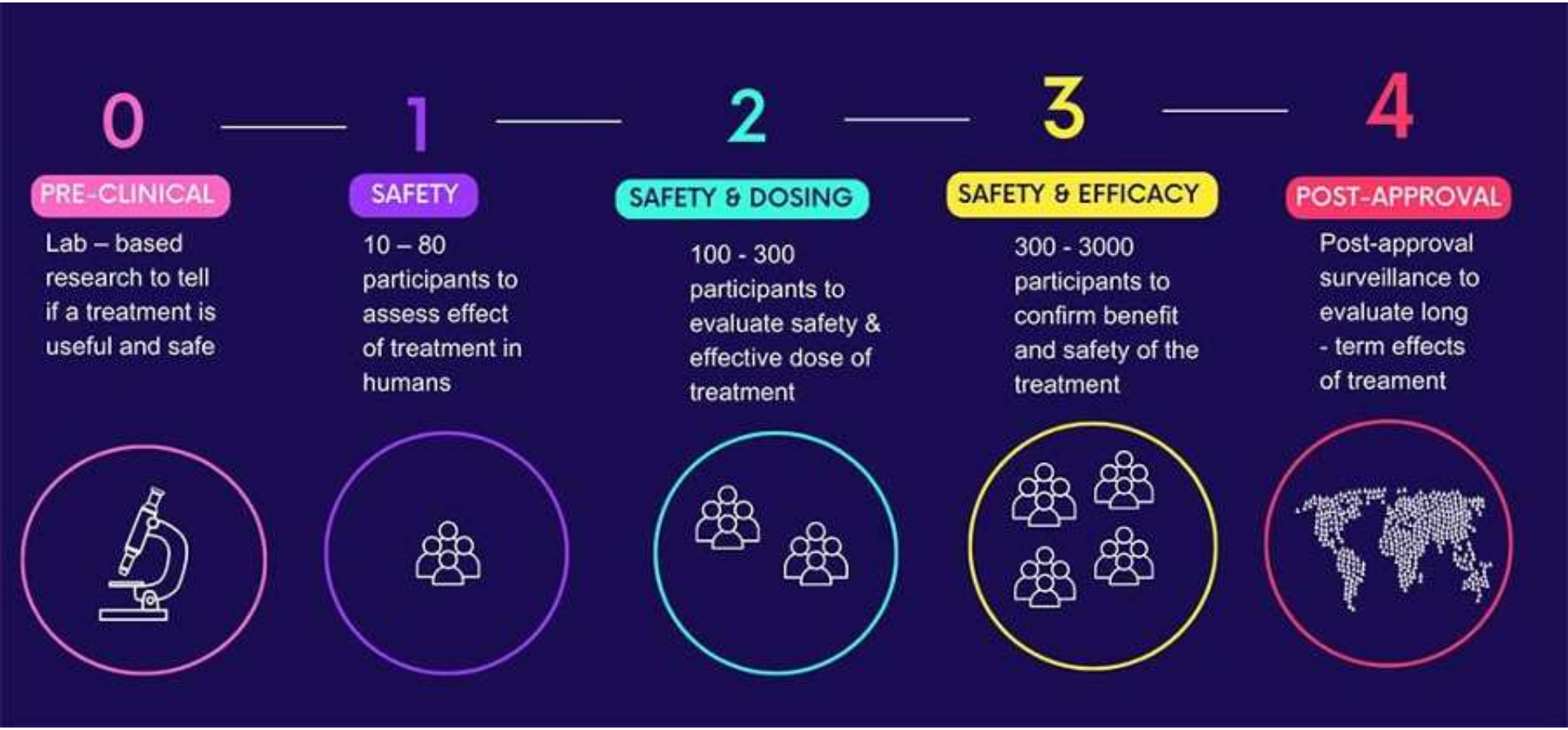
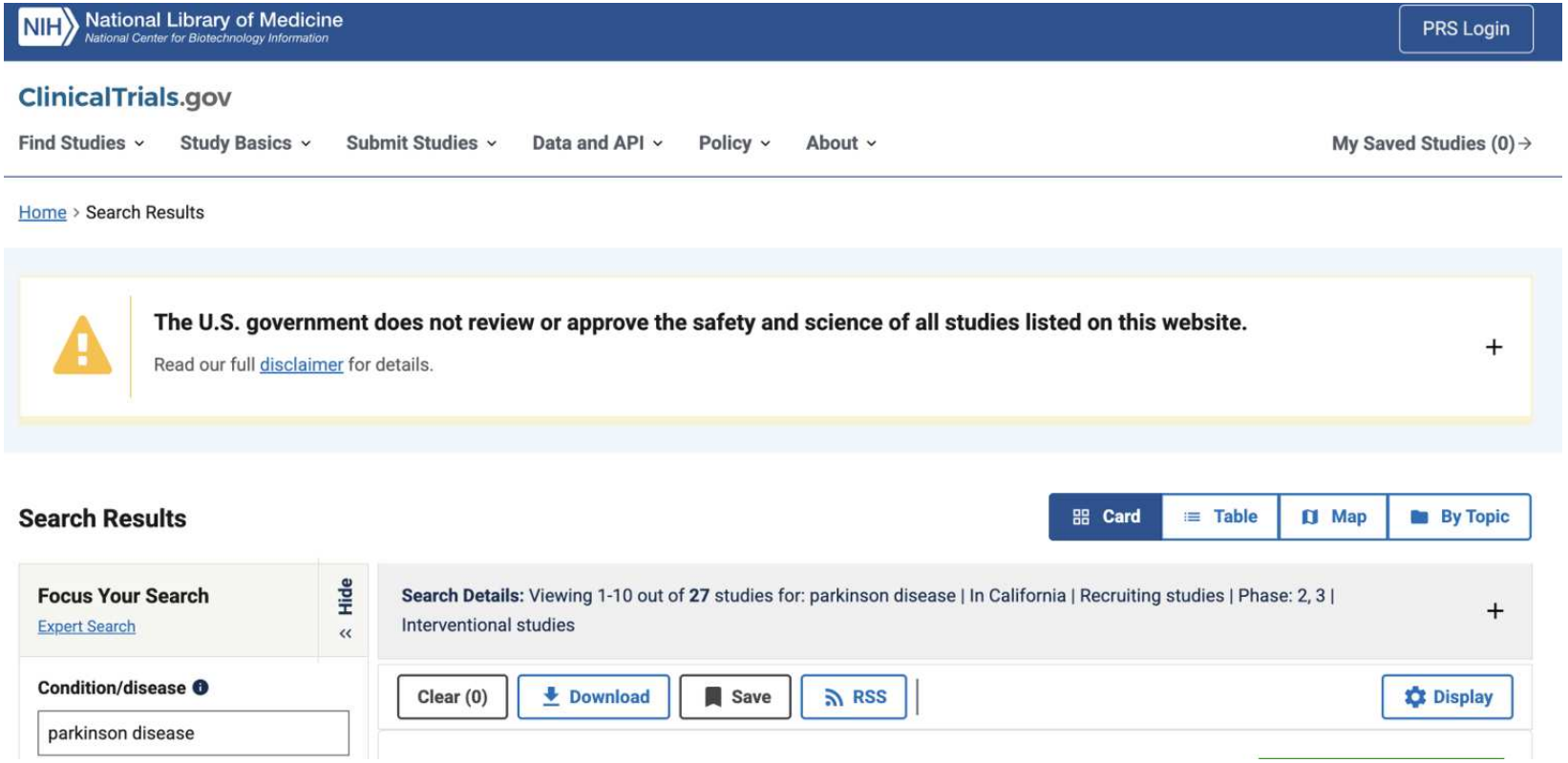
Stanford MEDICINE | School of Medicine

PHASES OF INTERVENTIONAL CLINICAL TRIALS

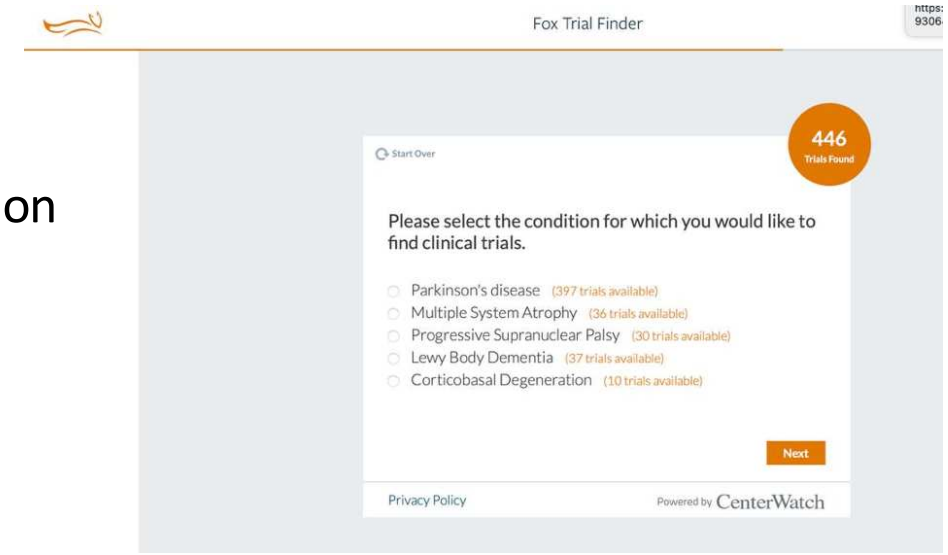


CURRENTLY AVAILABLE INTERVENTIONAL CLINICAL TRIALS FOR PD



RESOURCES FOR TRIALS AND THERAPIES

- Your Healthcare Team
- Local PD Support Groups
- American Parkinson Disease Association (APDA) www.apdama.org
- Michael J Fox Foundation www.foxtrialfinder.com
- NIH www.clinicaltrials.gov
- Center Watch www.centerwatch.com
- PSG www.parkinson-study-group.org
- PD Pipeline www.pdpipeline.org

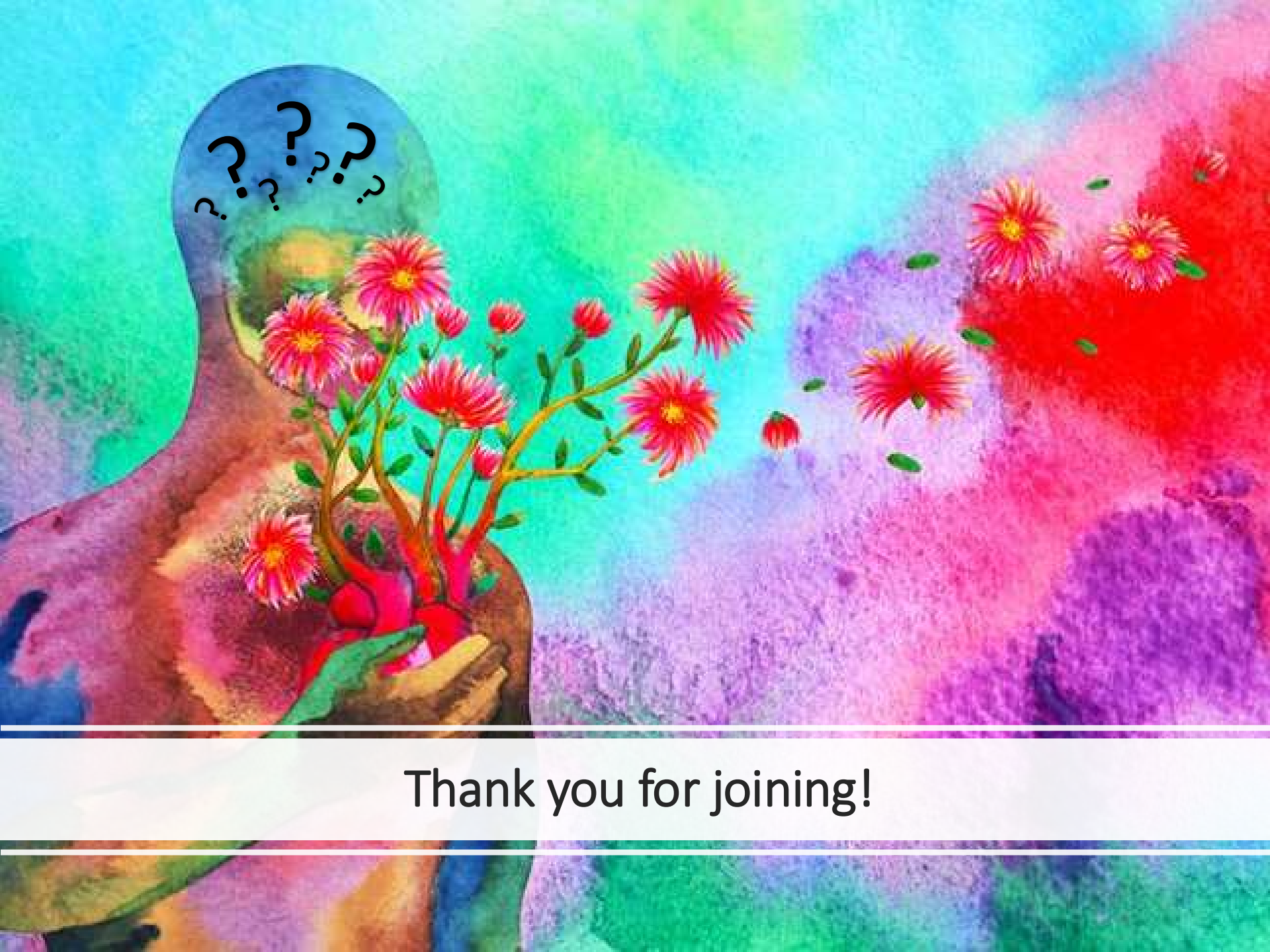


CURRENTLY AVAILABLE INTERVENTIONAL CLINICAL TRIALS IN CA

Sponsor	Trial	Type of treatment	phase	Location in CA
Kenai Therapeutics	RNDP-001	Intraputamenal Dopaminergic Stem Cell Transplants	1b/2	USC Keck
EicOsis Human Health Inc	STEP Study	Oral inhibitor of the enzyme, soluble epoxide hydrolase (sEH), as an anti-inflammatory agent	1/2	UC Davis
Neuron23 Inc	Neulark (NEU-411)	small molecule inhibitor of LRRK2 in LRRK2-driven PD	2	Multiple
AskBio Inc	REGENERATE-PD	Intraputaminal AAV2-GDNF	2	UCSF
Dr. Woolley, UCSF	Psilocybin	oral psilocybin therapy for depression	2	UCSF
SFVA, Dr. Bradley	Ketamine	Ketamine for depression in veterans with PD	2	SFVA
Biohaven	BHV-8000	Selective Brain-Penetrant TYK2/JAK1 Inhibitor (Neuroinflammation)	2/3	Los Angeles
Hoffmann-La Roche / Genentech	**PARAISO (Prasizunimab)**	**IV infusion of Anti-synuclein antibody**	**3**	**Multiple (Stanford)**
BlueRock Therapeutics	**ExPDite-2 (Bemdaneprocel)**	**Surgical implantation of human embryonic stem cell-derived midbrain dopaminergic neurons in the brain**	**3**	**Multiple (Stanford)**

Final thoughts and take-home points

- Parkinson's is Manageable
  - Many treatments options to improve quality of life
  - Symptoms and progression vary; but most people continue meaningful activities for MANY years after diagnosis
- Stay Active – Exercise is medicine!
- Build Your Care Team
- Address Non-Motor Symptoms
- Engage in Research that feels right for you
- Learn and Plan, but Live Today
- You Are Not Alone



Thank you for joining!