

Cure for PD: The Future of Treatment

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“When will we find a cure?”



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Barriers to Curing (and Even Treating) PD

- **Many known causes**
 - One patient likely has several
- **Many UNknown causes**
- **Complicated treatment goals**
 - Motor fluctuations
 - OFF episodes
- **Lack of oral route**
- **Not all treatments apply to all**
 - Eg, gene modifying therapies



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The “Root” of PD

- Aging
- Genetics
- Environmental exposures
- Diet
- Gut microbiome
- Exercise early in life

...and so much more!



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There is NO CURE for PD

Exercise is the only thing that delays disease progression

Focus on **symptomatic** management

Physical
Mental health
Medications
Surgery

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Why It's More Complicated

Heterogenous disease

- Tremor
- Akinetic-rigid
- Gait / Freezing
- Postural Instability
- Non-motor predominance

Complicating factors

- GI function / absorption
- Orthostasis
- Genetics
- DA dysregulation

Treatment goals

- Decrease medication burden
- Keep working
- Continue hobbies

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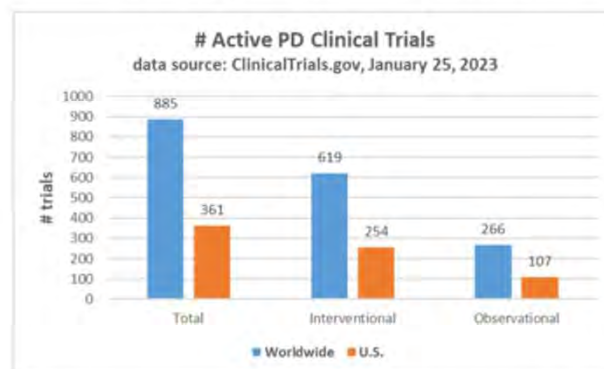
Future Directions of Treatment

- Disease-modifying (DMTs)
- Improving current treatment options
 - Medication delivery
 - Surgical techniques
- Problem-based approaches
 - Motor fluctuations
 - Gut absorption issues
 - Rescue therapies
 - Gait and balance
- Targeting biomarkers
- Database-centered observation

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PD Clinical Trial Tracker

Overview of Active PD Clinical Trials Worldwide

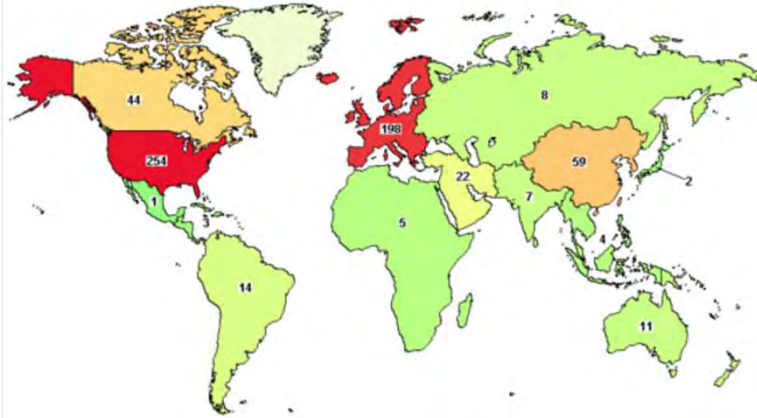


Note: Active PD trials are either i) currently recruiting, ii) not yet recruiting, iii) enrolling by invitation or iv) in-progress, not recruiting.

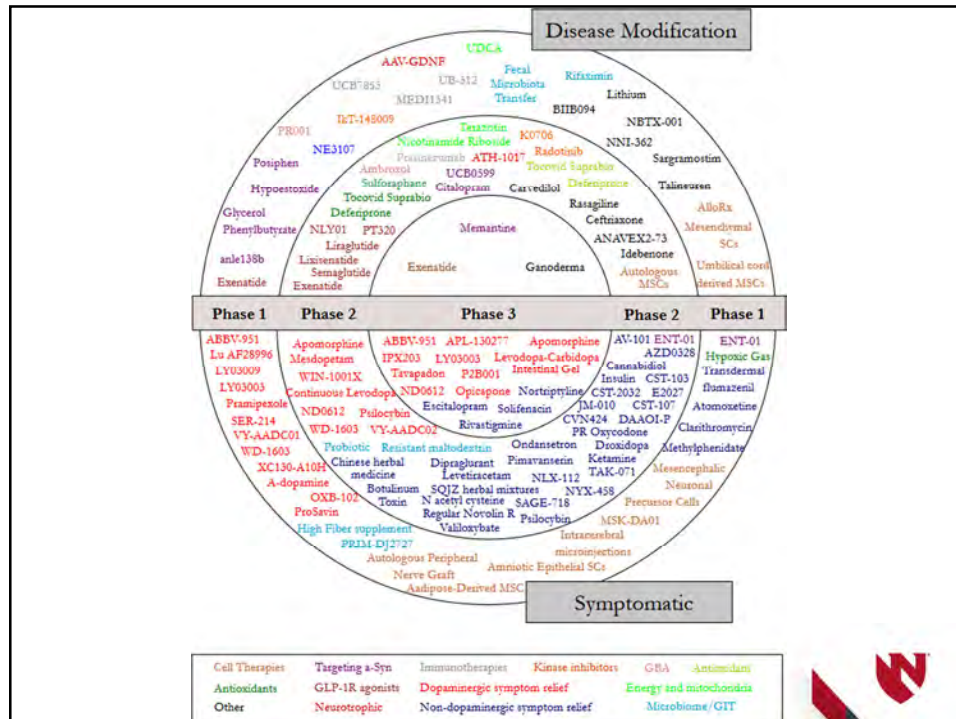
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PD Clinical Trial Tracker

Map View of 619 Active PD Interventional Trials
(map source: ClinicalTrials.gov, January 25, 2023)



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Table 2

Number of Trials by therapeutic category - ClinicalTrials.gov

Category	Phase 1		Phase 2		Phase 3		TOTAL
Anti-inflammatories	1	2.0%	0	0.0%	0	0.0%	1
Antioxidants	1	2.0%	2	2.7%	0	0.0%	3
Cell therapy	9	17.6%	2	2.7%	0	0.0%	11
Dopaminergic symptom relief	14	27.5%	9	12.2%	16	72.7%	39
Energy and mitochondria	1	2.0%	3	4.1%	0	0.0%	4
GBA	1	2.0%	1	1.4%	0	0.0%	2
GLP-1R agonists	1	2.0%	6	8.1%	1	4.5%	8
Immunotherapy	3	5.9%	2	2.7%	0	0.0%	5
Kinase inhibitors	1	2.0%	2	2.7%	0	0.0%	3
Microbiome/GIT	4	7.8%	2	2.7%	0	0.0%	6
Neurotrophic factors	2	3.9%	1	1.4%	0	0.0%	3
Non-dopaminergic symptom relief	2	3.9%	33	44.6%	3	13.6%	38
Targeting alpha-synuclein	5	9.8%	4	5.4%	1	4.5%	10
Other	6	11.8%	7	9.5%	1	4.5%	14
TOTAL	51		74		22		147

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Disease Modifying Treatments

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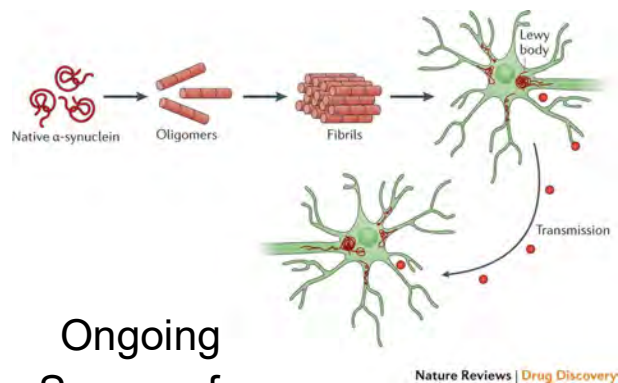
Mechanisms of DMTs

- Alpha synuclein targets
- Glucagon-like peptide (GLP-1) agonists
- Antioxidants
- Gene-specific
 - GBA
 - LRRK2

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Alpha Synuclein Therapies

- Antibodies
- Vaccines
- Aggregation “blockers”



Ongoing
Seem safe

→ But is it the **root** of PD?

Sheila M. Fleming, Ashley Davis, Emily Simons, Targeting alpha-synuclein via the immune system in Parkinson's disease: Current vaccine therapies, *Neuropharmacology*, Volume 202, 2022, 108870.

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GLP-1 Agonists

- Study suggested 30% risk of PD in pts with type 2 diabetes
- GLP-1 agonists = used to trigger insulin release
 - Receptors also present in the brain
 - GLP-1 agonists may block CNS “inflammatory response”
- Exenatide
 - modified form of exenatide designed for increased penetration into the brain
- Liraglutide
- Lixisenatide

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Oxidative Stress Models

- **Nilotinib**
 - C-Abl Kinase Inhibitor
 - Overactivation = downstream oxidative stress
 - Maybe related to alpha-synuclein aggregation
- Previously tested drugs had poor CNS penetration
- Improvements in progress

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GBA Gene Therapies

Glucocerebrosidase
(GBA)

GBA protein:
works in the
lysosome for cellular
breakdown

- Ambroxol
 - approved in Europe for respiratory illnesses, improves the function of GBA in neurons
- Venglustat
- Gene therapy trial which introduces the un-mutated GBA gene into the brain



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LRRK2 Gene Therapies

- LRRK2:
- Regulates alpha-synuclein & neuro-inflammation
 - Role in the endolysosomal system

- LRRK2 inhibitors
- LRRK2 antisense oligonucleotides



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Genes in Clinical Trials

- May be related to false negative or false positive results
 - eg, patients with GBA variants may have faster progression reflected in higher UPDRSR-III scores and H&Y staging

Machine learning model studies suggest genes =

better predictor of progression than imaging or CSF biomarkers



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How could this help us?

We could use certain faster progressing variants (eg GBA) to our advantage

Slower progression variants (LRRK2 maybe?) would have the opposite effect on clinical trials



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What about prodromal PD studies?

- Ideally you recruit these pts early as they would benefit the most from DMT
- PD has a well-established prodromal phase with research criteria
 - Now incorporates certain *GBA* and *LRRK2* variants
 - Both can exhibit prodromal PD features such as hyposmia, RBD, and dopaminergic loss on PET imaging

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Improving Symptomatic Treatments

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Forms of Levodopa

- Sinemet CR (extended release)

- Delayed onset
- Benefit in unpredictable
- Useful for overnight wearing off

- Rytary

- Capsule with microbeads
- Good for early wearing off



- Parcopa

- Dissolving tablet

- Inhaled powder (Inbrija)

- DUOPA intestinal gel

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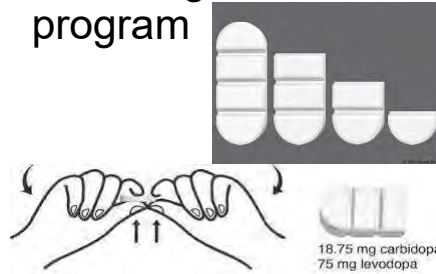
Parcopa

Sublingual
Swallowed with saliva
Can be taken without water

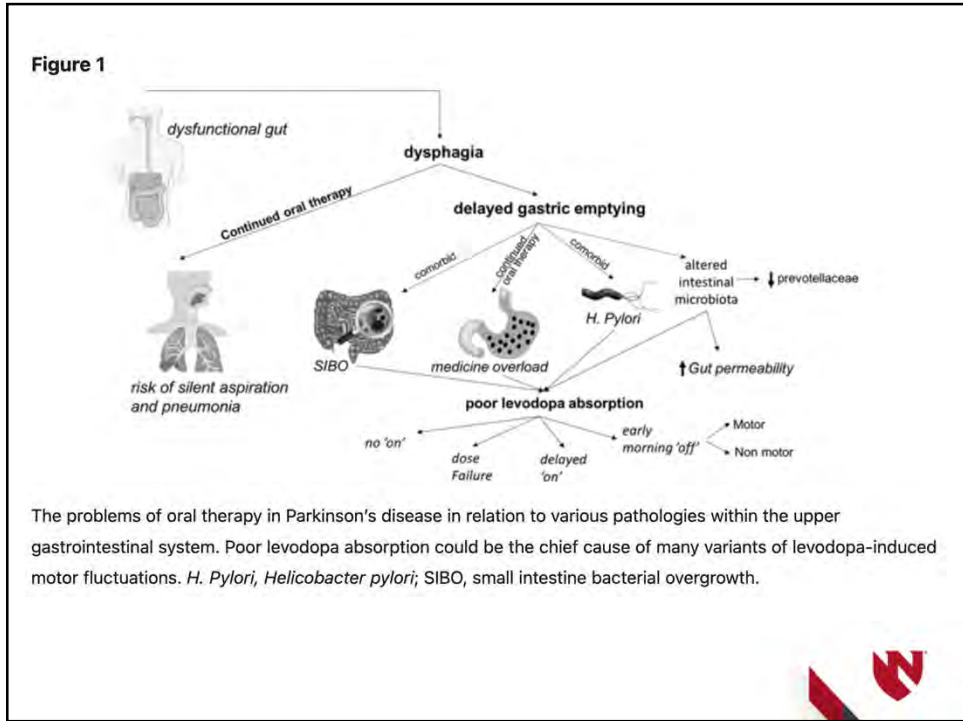


Dhivy

Allows 25 mg dosing (1/4 tablet) increments
\$\$, has grant program



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Inbrija

NEC K114-340-65

Inbrija
(levodopa inhalation powder)
For Oral Inhalation Only

42 mg CAPSULES

Do not swallow the capsules.

Inbrija
(levodopa inhalation powder) **Inbrija**
(levodopa inhalation powder)

For Oral Inhalation Only
Full Dose = 2 Capsules

42 mg per capsule + 42 mg per capsule

© 2019 GS

FDA approved 2018

- **Rescue therapy**
- 42 mg capsules
 - 1-2 caps per dose
- Use up to 5x daily

Advantages:

- Absorbed through pulmonary system
 - Bypass GI
- Rapid onset (10-15 min)

Disadvantages:

- Requires education
- Needs good/strong breath
- SEs: Cough, nausea, dizziness

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.

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Apomorphine

- Cannot be taken orally
 - Apokyn injectable
 - Kynmobi SL (2020)
 - SubQ infusion studied here but already in Europe
- Rescue therapy
 - Strongest agonist, can mimic levodopa – D1 and D2
 - High nausea risk



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Levodopa Infusions

Levodopa Continuous Intestinal Gel (LCIG)

“DUOPA Drama!”

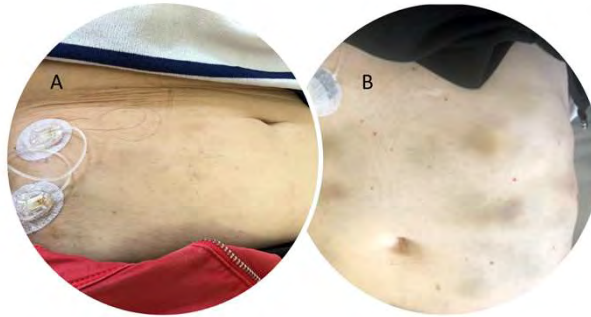
SubQ pump next in line?



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ABBV-951 (foslevodopa/foscarbidopa)

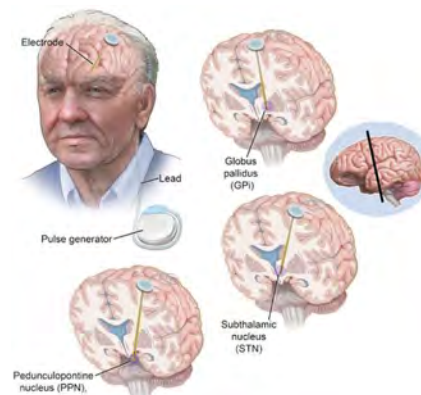
- FDA application pending with AbbVie (May 2022)



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Deep Brain Stimulation

- Being studied for early PD
- Sleep studies
- New anatomical targets
- Improvements in lead models
- Improvements in batteries
 - Collect data on symptoms
 - Optimized programming settings
- Better programming interfaces
 - Image-guided
 - Takes out “guess work”



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Focused Ultrasound

- FDA approved non-surgical treatment
- Unilateral
- Same day procedure in some cases



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Focused Ultrasound

Parkinson's disease tremor (neuromodulation)

A **clinical trial** in Los Angeles is using transcranial ultrasound neuromodulation to treat patients with essential tremor.

Parkinson's dyskinesia (unilateral pallidotomy)

This international pivotal trial has completed enrollment of patients.

Parkinson's disease (Staged unilateral or bilateral pallidothalamic tractotomy [PTT])

This trial has completed enrollment of patients.

Parkinson's dyskinesia (unilateral subthalamotomy)

This trial has completed enrollment of patients.

Parkinson's dyskinesia (unilateral subthalamotomy)

This trial is recruiting patients with movement disorders in Osaka, Japan.

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What about the Parkinson's Gloves ???

Featured on Good Morning America (December 2022)

Stanford Medicine
Peter Tass Labs



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The Parkinson's Gloves

- Still in clinical trials
 - 6 participants said it helped tremors, stiffness
- Vibration in fingertips
 - "Resets" abhorrent electrical activity in the brain
- FDA approval may not be for a few years



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“How Do I Get Involved?”



Visit clinicaltrials.gov



Call or email the **UNMC Research Advocate Office**

unmcrsa@unmc.edu

402-559-6941



Reference the **UNMC Clinical Trial Database:**

https://net.unmc.edu/ctsearch/index_unmc.php

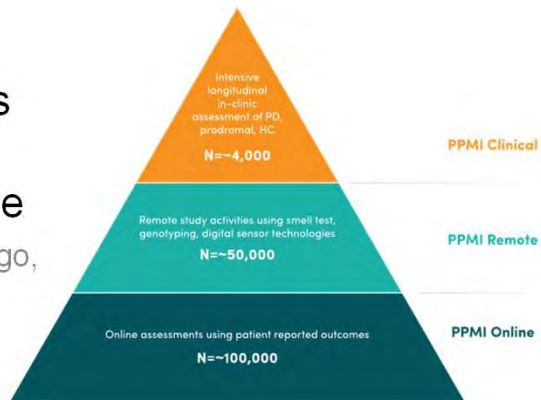
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PPMI



Parkinson's
Progression
Markers
Initiative

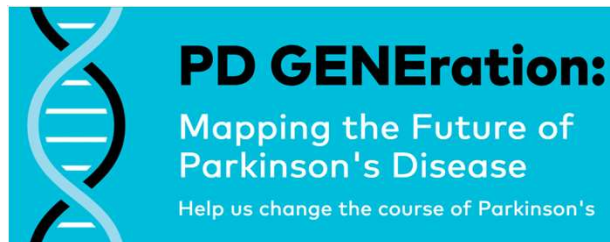
- Michael J. Fox Foundation
- No PD diagnosis needed
- Fill out info online
 - Local: KC, Chicago, Denver
- Data accessible upon request



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PD GENERation

- Michael J. Fox Foundation
 - Need PD diagnosis
 - In-person or remote options
 - We are an enrolling site
1. Screening visit (15-30 min)
 2. PD GENERation appointment (2 hours)
 1. Clinical assessments and cheek swab
 3. Genetic counselor consultation (15-30 min)
 1. Receive and review test results



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References

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- Soileau MJ et al. Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: A randomised, double-blind, active-controlled, phase 3 trial. *Lancet Neurol* 2022 Dec; 21:1099.
- Trial of Globus Pallidus Focused Ultrasound Ablation in Parkinson's Disease; The New England Journal of Medicine Massachusetts Medical Society Feb 23, 2023

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