

THIS IS NOT YOUR GRANDMOTHER'S DISEASE: WHAT DOES BEING DIAGNOSED WITH PARKINSON'S DISEASE MEAN TODAY?

THURSDAY MARCH 14, 2019

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VICE PRESIDENT, CHIEF SCIENTIFIC OFFICER, APDA



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ASSOCIATION**

Strength in optimism. Hope in progress.

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OUTLINE

- Overview of Parkinson's disease
- How are new treatments developed?
- Treatments in the pipeline

PARKINSON'S DISEASE: OVERVIEW

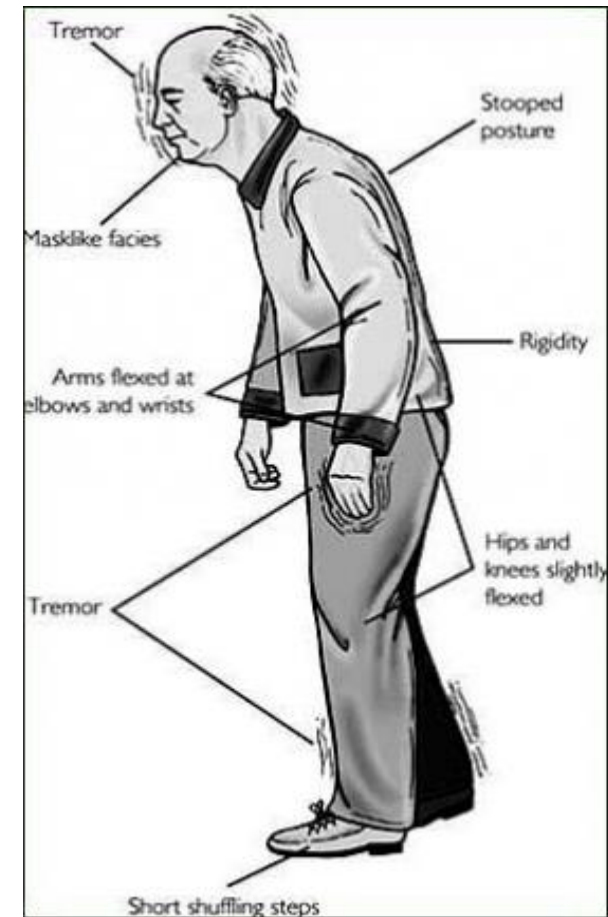


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MOTOR FEATURES OF PARKINSON'S DISEASE

- T** Tremor
- R** Rigidity
- A** Akinesia or Bradykinesia
- P** Postural instability



NON MOTOR FEATURES OF PARKINSON'S DISEASE

An iceberg floating in the ocean. The tip of the iceberg is above the water line, and the much larger base is submerged below the water line. The text is arranged around the iceberg, with the title above it and three categories of non-motor symptoms listed on either side of the submerged portion.

Non motor symptoms

NEUROPSYCHIATRIC

- Depression
- Sleep disorders
- Cognitive impairment and dementia
- Apathy

AUTONOMIC & VISCERAL

- Orthostatic hypotension
- Constipation
- Urinary dysfunction
- Sexual dysfunction

SENSORY

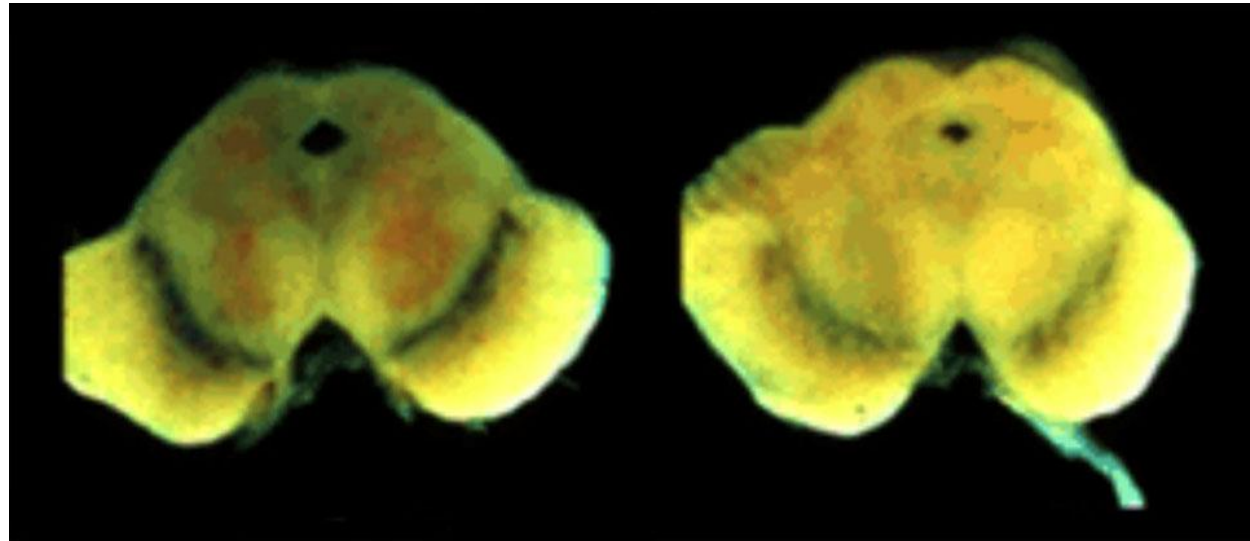
- Visual
- Loss of smell
- Pain



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MOTOR SYMPTOMS ARE CAUSED BY LOSS OF NERVES THAT PRODUCE DOPAMINE

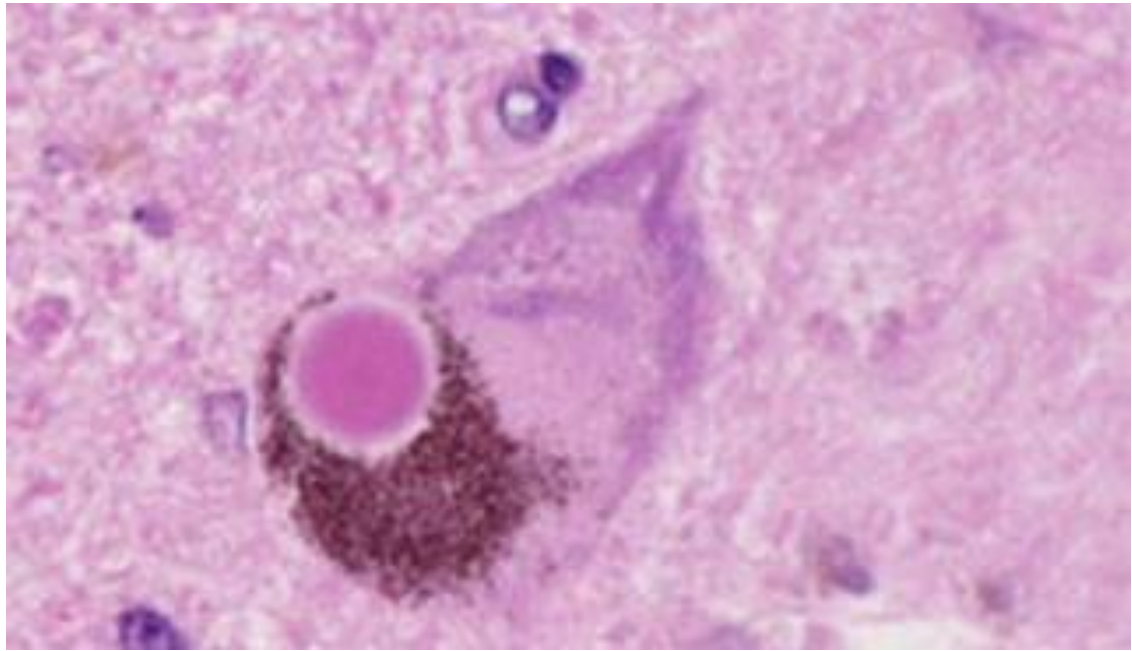


control

Parkinson's disease

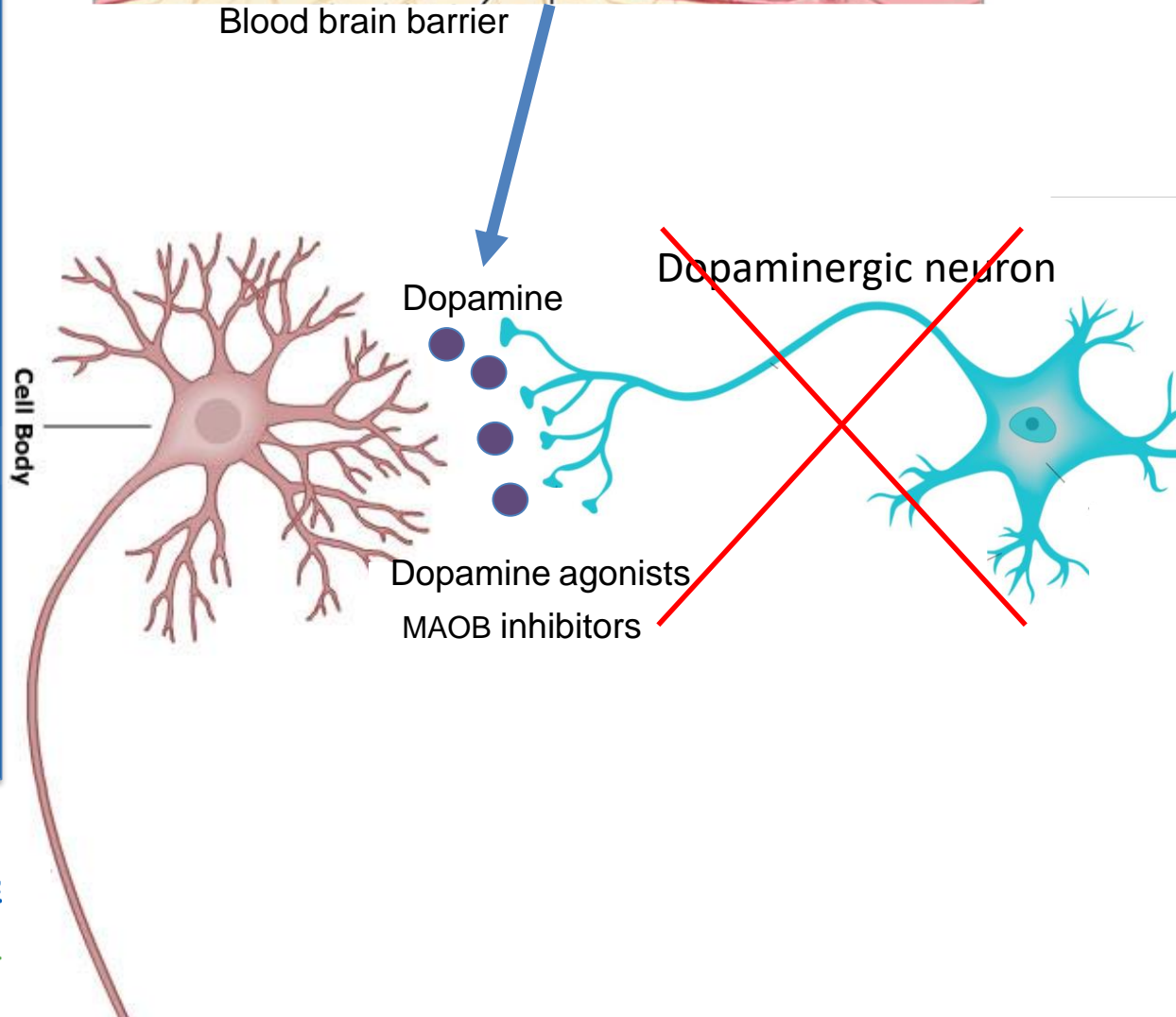
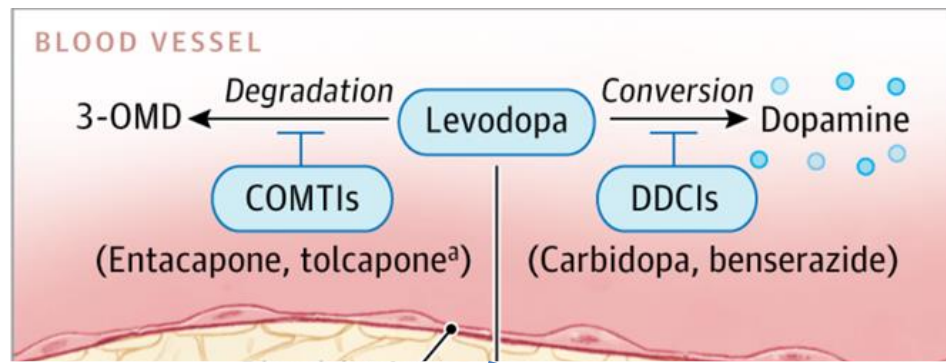
THE LEWY BODY

Alpha-synuclein:
Abnormal
accumulation in
Lewy bodies
is harmful to nerve
cells



AVAILABLE TREATMENTS FOR MOTOR SYMPTOMS:

- Levodopa formulations
- Dopamine agonists (pramipexole, ropinirole, rotigotine)
- MAOB inhibitors (selegiline, rasagiline, safinamide)
- COMT inhibitors (entacapone, tolcapone)
- Amantadine, amantadine ER
- Anticholinergics
- Deep brain stimulation



AVAILABLE PHARMACOLOGIC TREATMENTS FOR NON-MOTOR SYMPTOMS

Medications specifically indicated for Parkinson's disease:

Cognitive impairment: rivastigmine

Orthostatic hypotension: droxidopa

Parkinson's disease psychosis: pimavanserin



EXERCISE IN PD

Evidence supports the following claims (Neurology. 2011;77(3):288-94):

- Cardiovascular fitness is associated with better cognitive and motor scores in PD
- Longevity in PD is associated with increased physical activity
- Non motor features of PD such as constipation, fatigue, depression, all improve with exercise and fitness



HOW ARE NEW TREATMENTS DEVELOPED?



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HOW DO NEW TREATMENTS COME TO BE?

Preclinical development – testing in cell culture, animal models, etc

Phase I: testing in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

Phase II: testing in a larger group of people to see if it is effective and to further evaluate its safety.

Phase III: testing in a large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments

Phase IV: Testing after the treatment is approved, to gather more information on side effects.

APDA SCIENTIFIC ADVISORY BOARD

Dr. Joel
Perlmutter

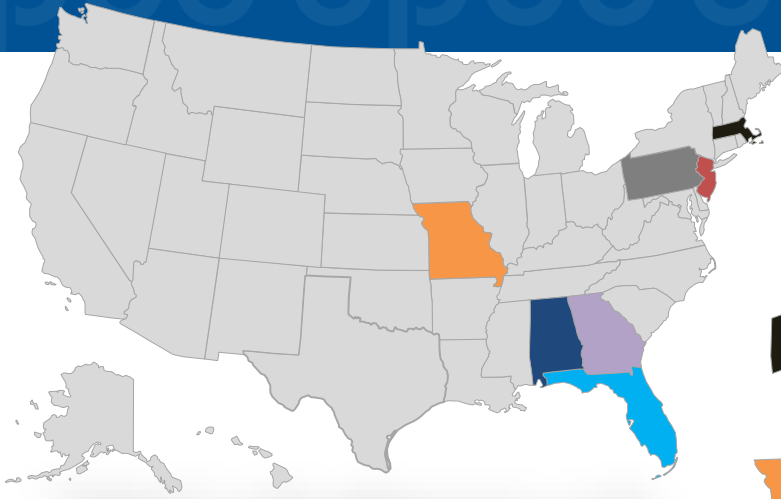


The goal: to bring the best new talent to the field of PD research

APDA Research 2018-2019

- Summer Student Fellowships (APDA in collaboration with Parkinson's Foundation) – 12 awarded
- Post-Doctoral Fellowships – 2 awarded
- Research Grants – 11 awarded
- Dr. George C. Cotzias Memorial Fellowship – 1 awarded (and 1 in third year of award)
- APDA Centers for Advanced Research in Parkinson's Disease – 8 awarded

APDA CENTERS FOR ADVANCED RESEARCH



Boston University – Marie Saint-Hilaire, MD, Director



Harvard Medical School and Brigham and Women's Hospital – Clemens Scherzer, MD Director



Washington University – Joel S. Perlmutter, MD, Director



University of Alabama at Birmingham – David Standaert, MD, PhD, Director



Rutgers Robert Wood Johnson Medical School – M. Maral Mouradian, MD, Interim Director



Emory University – Thomas Wichmann, MD, Interim Director



University of Pittsburgh – J. Timothy Greenamyre, MD, PhD, Director



Mayo Clinic Jacksonville
Dennis Dickson MD, Director

SELECT APDA 2018-2019 GRANTS



Roberta Marongiu, PhD
Weill Cornell Medicine

Menopause as an important transition state in the susceptibility to PD

Studying PD pathology in a mouse model of menopause



Mallory Hacker, PhD
Vanderbilt University Medical Center
Investigating Long-Term Clinical Outcomes of Subthalamic Nucleus Deep Brain Stimulation (DBS) in Early Stage PD

Studying patients who received DBS in early PD to determine the long-term effects of DBS done in this unique population.

TREATMENTS IN THE PIPELINE

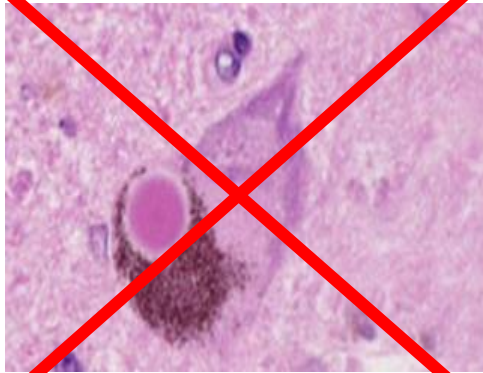


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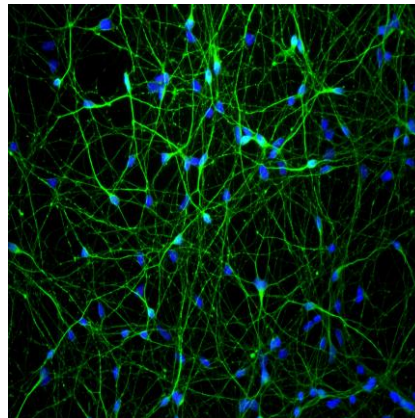
Strength in optimism. Hope in progress.

PARKINSON'S DISEASE: HOW TO SOLVE THE PROBLEM?

Abnormal accumulation of alpha-synuclein into Lewy bodies causes cell death resulting in lack of dopamine which causes problems with movement. So...



Stop Lewy body
formation



Enhance
cell survival



Introduce
dopamine
in new ways

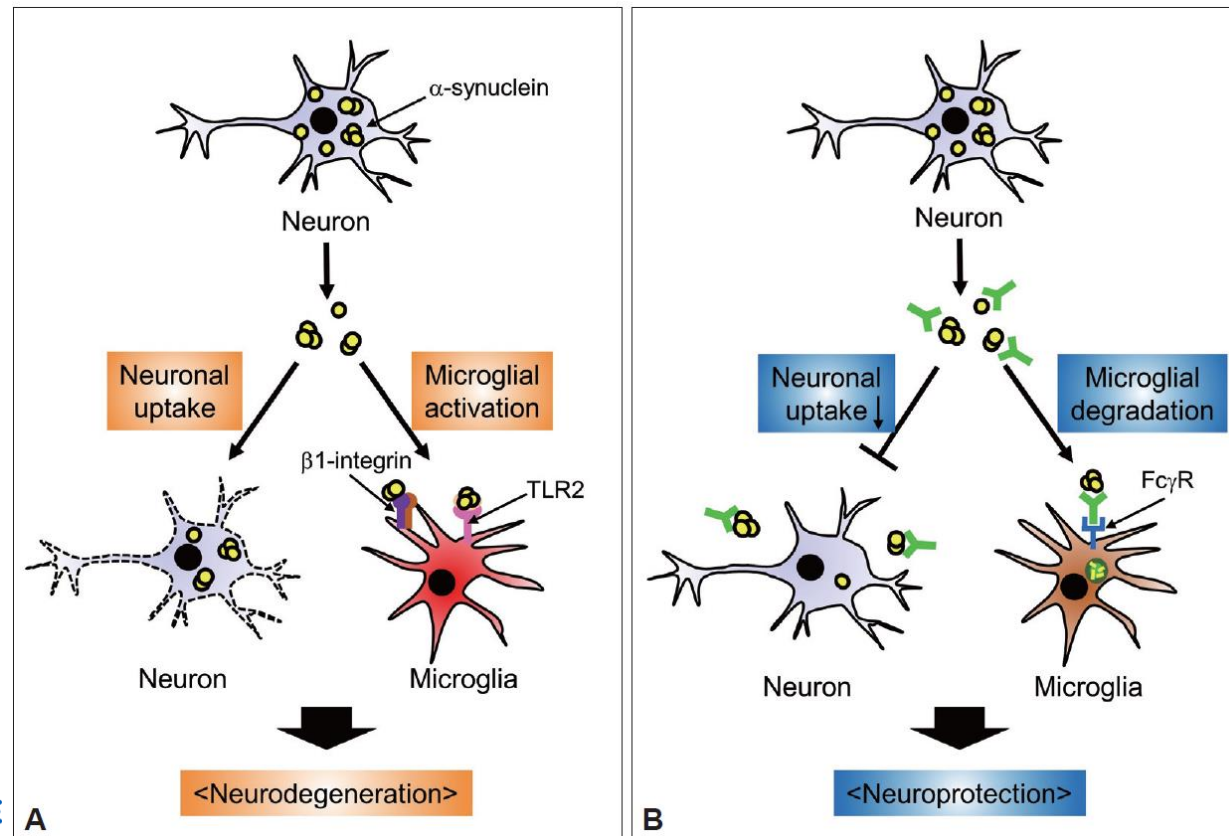
PARKINSON'S DISEASE: HOW TO SOLVE THE PROBLEM?

- A. Removing/inhibiting alpha-synuclein aggregation
- B. Neuroprotective strategies
- C. Mutation specific strategies
- D. Dopamine delivery systems

ALPHA-SYNUCLEIN VACCINATION

- Injection of peptides which induce immune responses against alpha-synuclein (active immunity)
- IV infusion of alpha-synuclein antibodies (passive immunity)

J Mov Disord 2016; 9(1):
14-19.



PREVENTING OR DESTROYING ALPHA-SYNUCLEIN CLUMPS

Nilotinib

- An inhibitor of the tyrosine kinase Bcr-abl, approved for use in chronic myelogenous leukemia.
- Pre-clinical work showed that nilotinib can induce regulated destruction of alpha-synuclein without destroying the neuron
- A Phase 2 trial with a placebo arm and enrollment goal of 75 patients is underway

New compounds are in development which bind to alpha-synuclein and block its accumulation

PARKINSON'S DISEASE: HOW TO SOLVE THE PROBLEM?

A. Removing/inhibiting alpha-synuclein aggregation

B. Neuroprotective strategies

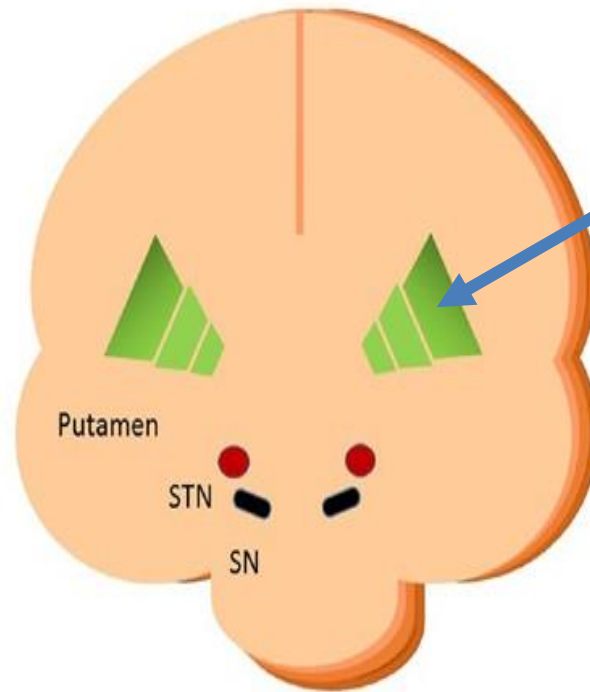
C. Mutation specific strategies

D. Dopamine delivery systems

ISRADIPINE (DYNACIRC)

- Isradipine is a calcium channel blocker, approved for high blood pressure
- Epidemiologically, patients on calcium channel blockers had lower risk of PD
- Isradipine protected dopaminergic cells from oxidative damage in cell culture
- Phase II trial (STEADY-PD) showed safety in PD patients and established the dose at 5 mg twice a day
- A Phase III (3 year) trial completed enrollment and results are expected in 2019

GLIAL CELL LINE DERIVED NEUROTROPHIC FACTOR (GDNF) THERAPY

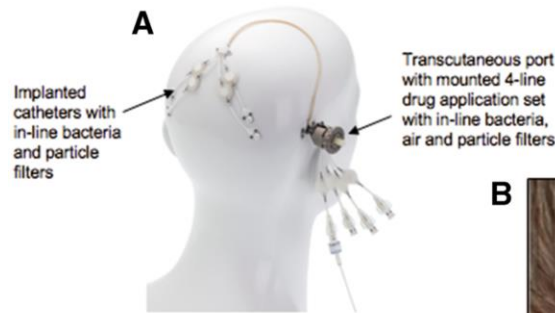


GDNF infusion

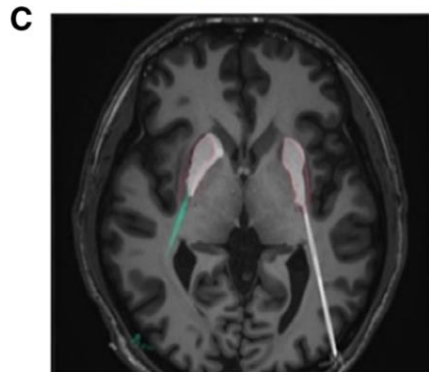
AAV2-GDNF (phase I, open-label)

clinicaltrials.gov/ct2/show/NCT01621581

GLIAL CELL LINE DERIVED NEUROTROPHIC FACTOR (GDNF) THERAPY



Drug delivery system used in study



Gadolinium test infusion



Skull-mounted port



Patient receiving infusion



GDNF study Infusion suite

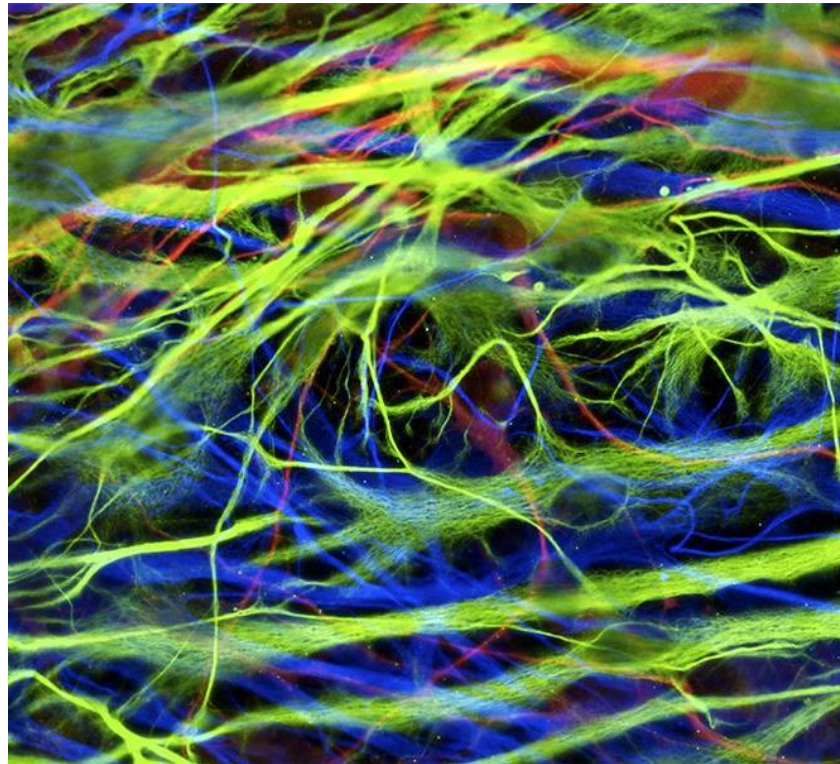
Brain, Volume 142, Issue 3, 26 February 2019, Pages 512–525, <https://doi.org/10.1093/brain/awz023>

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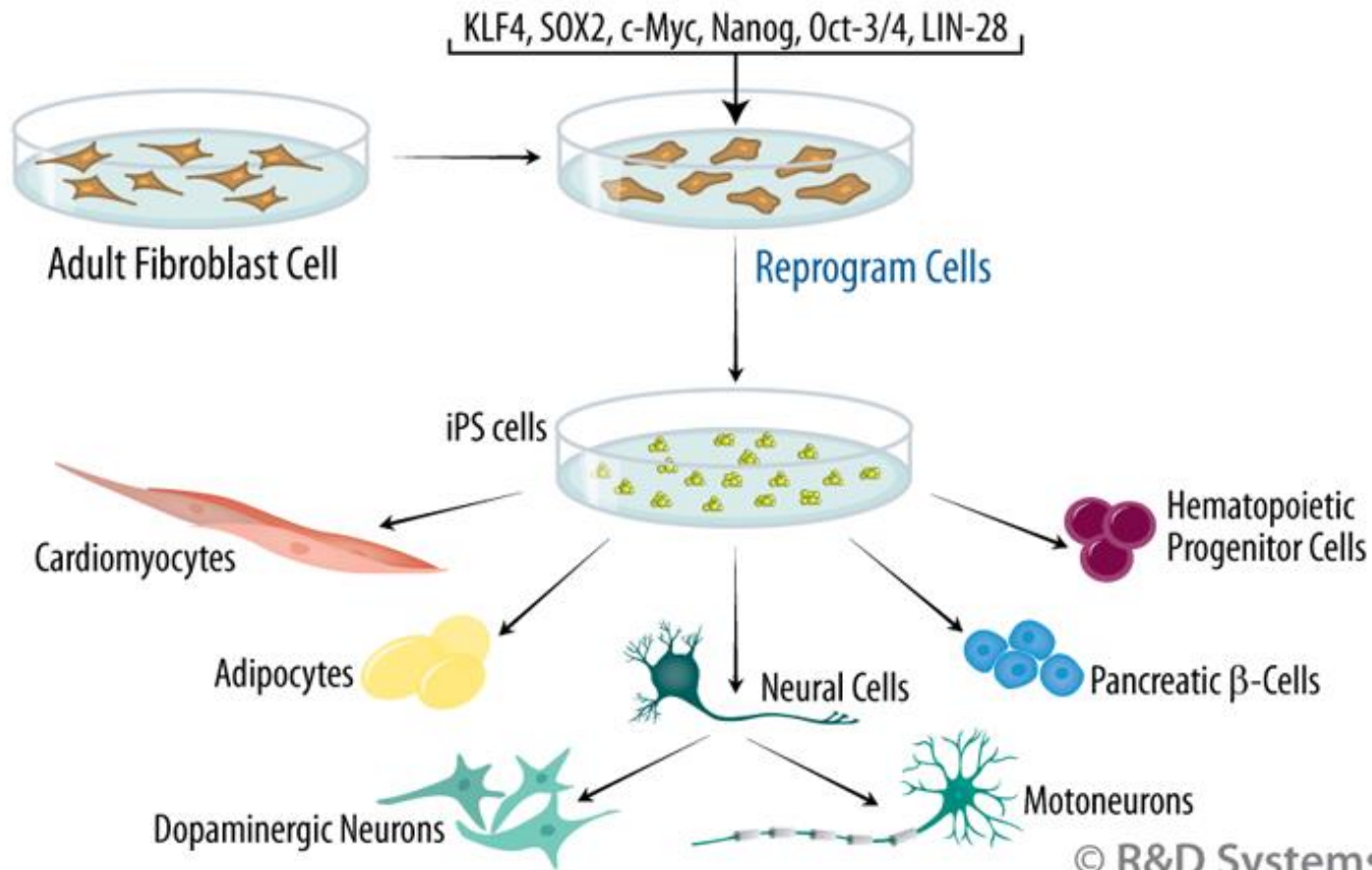
OXFORD
UNIVERSITY PRESS

STEM CELL THERAPY

A clinical trial in Japan is underway in which dopamine precursor cells are implanted into the brains of people with PD. These dopamine precursor cells are derived from induced pluripotent stem cells



STEM CELL THERAPY

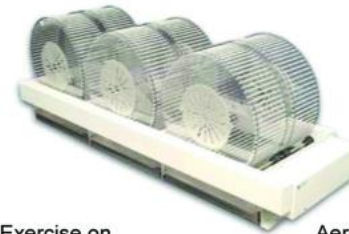


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EXERCISE AND PARKINSON'S DISEASE

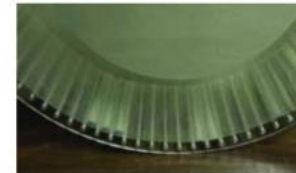
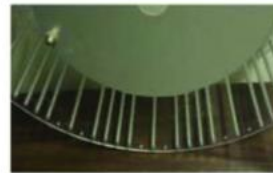
J Hum Kinet. 2016
Sep 1; 52: 35–51.

Learn a new motor skill!

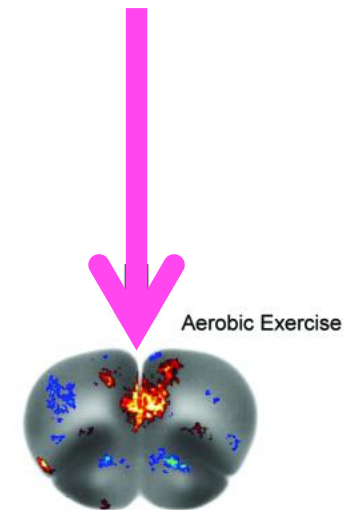


Skilled Exercise on
Complex Wheel

Aerobic Exercise on
Simple Wheel



Elevated regional
Cerebral Blood flow in
medial regions (PFC) and
dorsal medial regions
(motor M1, M2)



Limited regional
Cerebral Blood flow in
medial regions (PFC) and
dorsal medial regions
(motor M1, M2)

PARKINSON'S DISEASE: HOW TO SOLVE THE PROBLEM?

A. Removing/inhibiting alpha-synuclein aggregation

B. Neuroprotective strategies

C. Mutation specific strategies

D. Dopamine delivery systems

Continuous delivery

On demand delivery

GLUCOCEREBROSIDASE AND PARKINSON'S DISEASE



The NEW ENGLAND
JOURNAL of MEDICINE

HOME ARTICLES & MULTIMEDIA ▾ ISSUES ▾ SPECIALTIES & TOPICS ▾ FOR AUTHORS ▾ CME ▸

ORIGINAL ARTICLE

Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson's Disease

E. Sidransky, M.A. Nalls, J.O. Aasly, J. Aharon-Peretz, G. Annesi, E.R. Barbosa, A. Bar-Shira, D. Berg, J. Bras, A. Brice, C.-M. Chen, L.N. Clark, C. Condroyer, E.V. De Marco, A. Dürr, M.J. Eblan, S. Fahn, M.J. Farrer, H.-C. Fung, Z. Gan-Or, T. Gasser, R. Gershoni-Baruch, N. Giladi, A. Griffith, T. Gurevich, C. Januario, P. Kropp, A.E. Lang, G.-J. Lee-Chen, S. Lesage, K. Marder, I.F. Mata, A. Mirelman, J. Mitsui, I. Mizuta, G. Nicoletti, C. Oliveira, R. Ottman, A. Orr-Urtreger, L.V. Pereira, A. Quattrone, E. Rogava, A. Rolfs, H. Rosenbaum, R. Rozenberg, A. Samii, T. Samadpour, C. Schulte, M. Sharma, A. Singleton, M. Spitz, E.-K. Tan, N. Tayebi, T. Toda, A.R. Troiano, S. Tsuji, M. Wittstock, T.G. Wolfsberg, Y.-R. Wu, C.P. Zabetian, Y. Zhao, and S.G. Ziegler
N Engl J Med 2009; 361:1651-1661 | [October 22, 2009](#) | DOI: 10.1056/NEJMoa0901281



Molecular Genetics and Metabolism

Volume 73, Issue 4, August 2001, Pages 313-321



Regular Article

Gaucher Disease and Parkinsonism: A Phenotypic and Genotypic Characterization

N. Tayebi^a, M. Callahan^a, V. Madike^a, B.K. Stubblefield^a, E. Orvisky^a, D. Krasnewich^a, J.J. Fillano^b, E. Sidransky^{a,1}



[Brain](#). 2015 Sep; 138(9): 2648-2658.

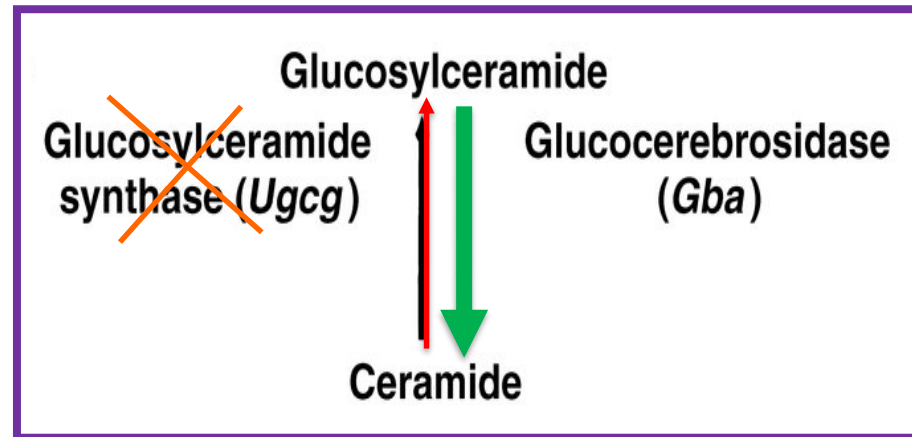
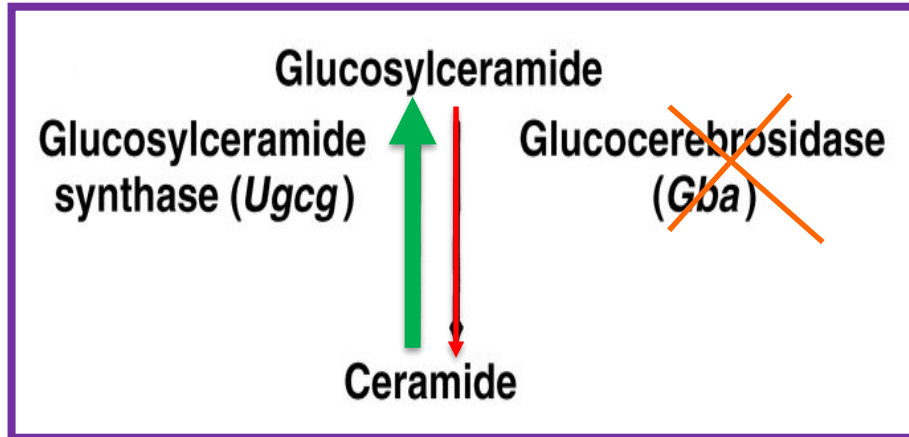
PMCID: PMC4564023

Published online 2015 Jun 27. doi: [10.1093/brain/awv179](#)

Glucocerebrosidase activity in Parkinson's disease with and without *GBA* mutations

[Roy N. Alcalay](#),^{1,2} [Oren A. Levy](#),^{1,2} [Cheryl C. Waters](#),¹ [Stanley Fahn](#),¹ [Blair Ford](#),¹ [Sheng-Han Kuo](#),¹ [Pietro Mazzoni](#),¹ [Michael W. Pauciulo](#),³ [William C. Nichols](#),³ [Ziv Gan-Or](#),⁴ [Guy A. Rouleau](#),⁴ [Wendy K. Chung](#),⁵ [Pavlina Wolf](#),⁶ [Petra Oliva](#),⁶ [Joan Keutzer](#),⁶ [Karen Marder](#),^{1,2,7} and [Xiaokui Zhang](#)⁶

GBA SPECIFIC THERAPIES



- Enzyme-replacement therapy is used to treat Gaucher's disease but does not cross the blood brain barrier.
- The same effect could be obtained by inhibition of glucosylceramide synthase (GCS)
<https://clinicaltrials.gov/ct2/show/NCT02906020>

LRRK2 SPECIFIC THERAPIES

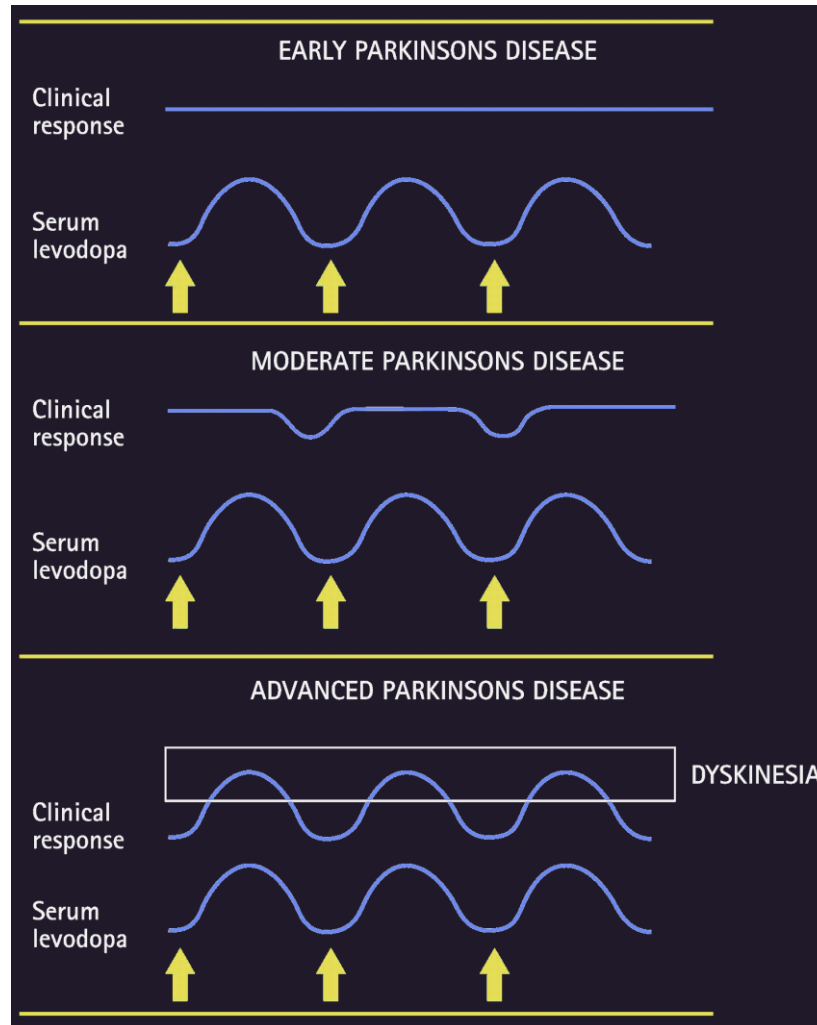
- LRRK2 is a kinase - it adds phosphate groups onto other proteins.
- Mutations in LRRK2 that cause PD, increase the activity of LRRK2.
- A small molecule which inhibits the activity of LRRK2 is currently in clinical trials.

<https://clinicaltrials.gov/ct2/show/NCT03710707>

PARKINSON'S DISEASE: HOW TO SOLVE THE PROBLEM?

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DOPAMINE DELIVERY SYSTEMS

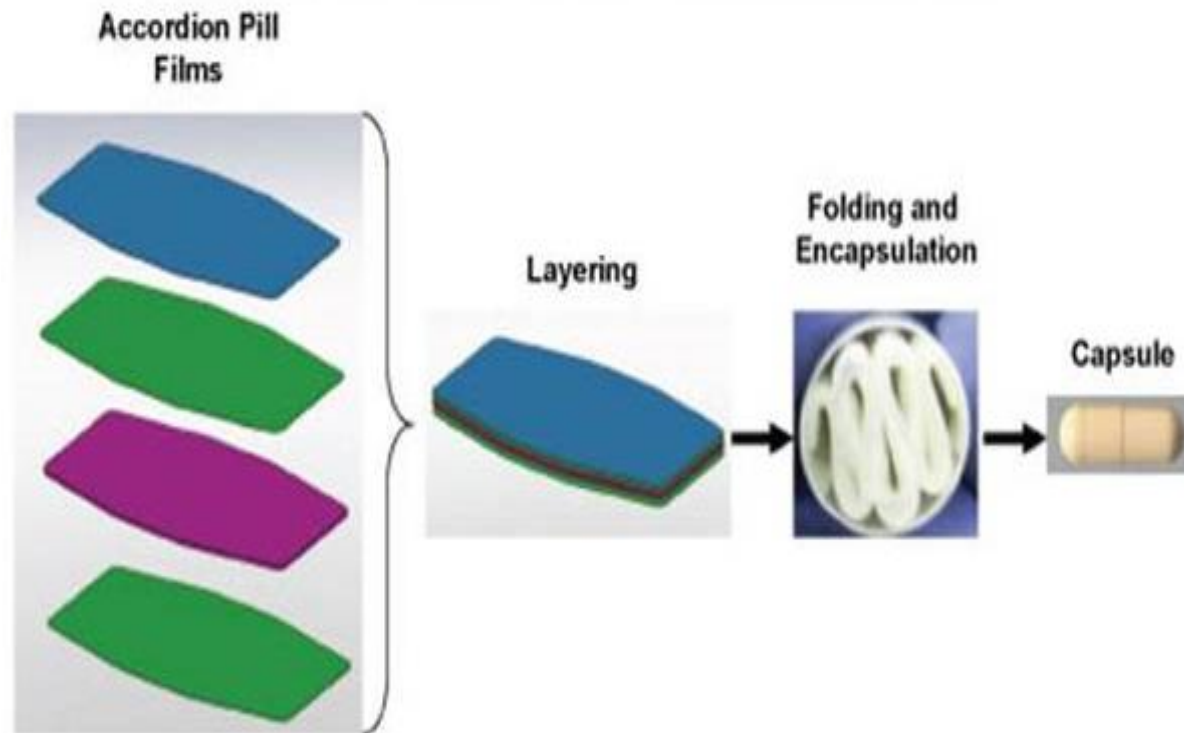


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ACCORDION PILL

General Structure of the Accordion Pill



CARBIDOPA/LEVODOPA ACCORDION PILL (AC-CD/LD)

- Pill is retained in the stomach for 8-12 hours, as opposed to 2-3 hours
- This pill is useful for medications that are absorbed in the more proximal portions of the GI tract
- A Phase II trial showed a reduction of OFF time by 45% without an increase in, or with a reduction in, time with dyskinesias
- Current phase III trial:
clinicaltrials.gov/ct2/show/NCT02605434

OPICAPONE – NEW COMT INHIBITOR

- Currently available COMT inhibitors are Entacapone and Tolcapone. Tolcapone can cause liver failure which limits its use
- Phase III trial has been completed for opicapone and showed a decrease in OFF time (JAMA Neurology. 2016 Dec 27. doi: 10.1001/jamaneurol.2016.4703).

PARKINSON'S DISEASE: HOW TO SOLVE THE PROBLEM?

- A. Removing/inhibiting alpha-synuclein aggregation
 - Alpha-synuclein vaccines
 - Other molecules that prevent alpha-synuclein clumping
- B. Neuroprotective strategies
 - Isradipine
 - GDNF
 - Stem cell therapies
 - Exercise
- C. Mutation specific strategies
 - GBA
 - LRRK2
- D. Dopamine delivery systems
 - Accordion pill
 - New COMT inhibitor

THANK YOU!

1-800-223-2732

apdaparkinson.org

EXERCISE IN PD

- Other age-related problems can complicate PD. Don't add deconditioning to this list!
 - vestibular loss
 - neuropathy
 - spinal stenosis and lower back pain
 - arthritis
 - osteoporosis
 - prior strokes, etc. etc. etc.
- Even less vigorous activity can improve fall risk, (*Mov Disord.* 2010 Jul 15;25(9):1217-25) balance, and mobility (*Gait Posture.* 2008 Oct;28(3):456-60)



EXERCISE AND PARKINSON'S DISEASE

Patients were assigned to one of three exercise groups:

- High intensity treadmill use
- Low intensity treadmill use
- Stretching and resistance exercises

Findings

- Walking speed improved in low intensity treadmill group
- Gait and mobility improved in low and high intensity treadmill group
- Muscle strength improved in stretching and resistance group

Conclusion: combine workout types! The more the better!

JAMA Neurol. 2013 Feb;70(2):183-90