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
Strength in optimism. Hope in progress.
• Overview of Parkinson’s disease
• How are new treatments developed?
• Treatments in the pipeline
PARKINSON’S DISEASE: OVERVIEW
MOTOR FEATURES OF PARKINSON’S DISEASE

T Tremor
R Rigidity
A Akinesia or Bradykinesia
P Postural instability
NON MOTOR FEATURES OF PARKINSON’S DISEASE

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
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
Medications specifically indicated for Parkinson’s disease:

Cognitive impairment: rivastigmine

Orthostatic hypotension: droxidopa

Parkinson’s disease psychosis: pimavanserin
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?
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 group 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.
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
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
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)

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.
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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


AAV2-GDNF (phase I, open-label) clinicaltrials.gov/ct2/show/NCT01621581
GLIAL CELL LINE DERIVED NEUROTROPHIC FACTOR (GDNF) THERAPY


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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

https://www.rndsystems.com/resources/articles/differentiation-potential-induced-pluripotent-stem-cells
EXERCISE AND PARKINSON’S DISEASE

J Hum Kinet. 2016 Sep 1; 52: 35–51.

Learn a new motor skill!
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
Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson's Disease


Regular Article

Gaucher Disease and Parkinsonism: A Phenotypic and Genotypic Characterization

N. Tayebi1, M. Callahan1, V. Madike2, B.K. Stubblefield2, E. Orvisky2, D. Krasnewich2, J.J. Fillano3, E. Sidransky1

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

Roy N. Acalay1,2 Dren A. Levy1,2 Cheryl C. Waters1, Stanley Fahn3, Blair Ford4, Sheng-Han Kuo4, Pietro Mazzoni1, Michael W. Pauciulo1, William C. Nichols3, Ziv Gan-Or4, Guy A. Rouleau4, Wendy K. Chung5, Pavina Wolf6 Petra Oliva6, Joan Keutzer6, Karen Marder1,2,7 and Xiaokui Zhang8

BRAIN A JOURNAL OF NEUROLOGY

Published online 2015 Jun 27. doi: 10.1046/brainav179

PMCID: PMC4564923

GLUCOCEREBROSIDASE AND PARKINSON’S DISEASE
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

- **EARLY PARKINSONS DISEASE**
  - Clinical response
  - Serum levodopa

- **MODERATE PARKINSONS DISEASE**
  - Clinical response
  - Serum levodopa

- **ADVANCED PARKINSONS DISEASE**
  - Clinical response
  - Serum levodopa
  - Dyskinesia

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**AMERICAN PARKINSON DISEASE ASSOCIATION**
Strength in optimism. Hope in progress.
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
• 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