Parkinson's Disease

American Parkinson Disease Association
www.apdaparkinson.org

Spotlight on Addressing Motor and Non-Motor Symptoms – The Changing Landscape

Wednesday, March 8, 2017

Generously supported by: Joan and Ross Collard

Supported in part by a grant from: abbvie

Welcome and Introductions

Stephanie Paul
Vice President Development and Marketing
American Parkinson Disease Association

American Parkinson Disease Association
www.apdaparkinson.org

Presentation

David G. Standaert, MD, PhD
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The University of Alabama Birmingham School of Medicine
Chair, APDA Scientific Advisory Board

American Parkinson Disease Association
www.apdaparkinson.org

Disclosures

In the last year, Dr. Standaert has served as a consultant for

- AbbVie, Inc.
- Serina Therapeutics
- Voyager Therapeutics

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Parkinson Disease: 200th Anniversary

James Parkinson 1817

AN
ESSAY
ON THE
SHAKING PALSY.

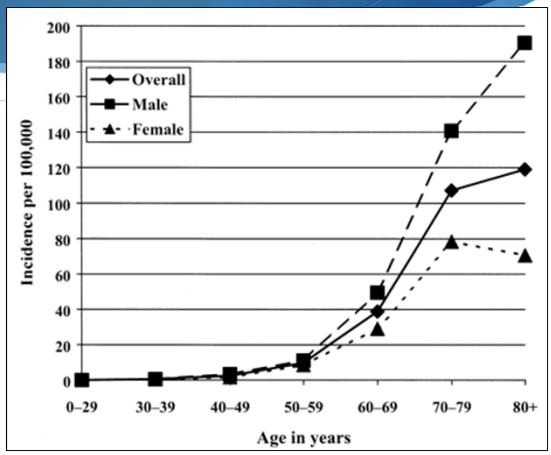
CHAPTER I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

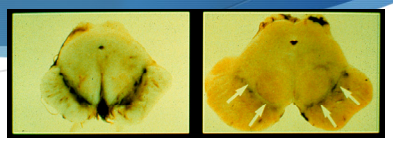
Age and Parkinson Disease

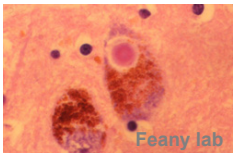
- ***The Good News:*** We are living longer. Most Americans alive today can expect to live to at least 80 years
- ***Not So Good News:*** The older we get, the more likely we are to get Parkinson's Disease

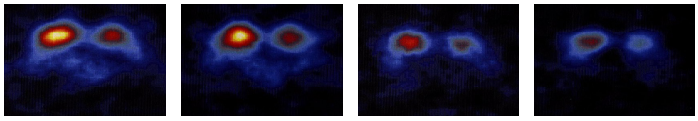


Classical Features of Parkinson Disease

- Rest Tremor
- Bradykinesia
- Rigidity
- Postural Imbalance







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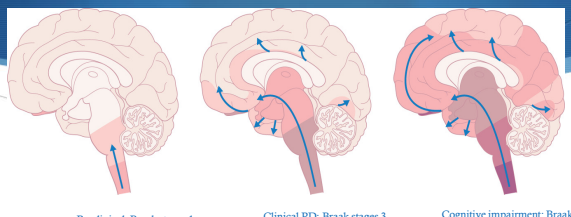
Parkinson Disease: Non-motor Features



Reproduced with permission from: Olanow et al. Neurology 2009;72(Suppl 4):S1–136 (© Wolters Kluwer Health)

- **Early (premotor) Features**
  - **Hyposmia** – loss of the sense of smell
  - **REM Behavior Disorder** – "acting out dreams"
  - **Autonomic disturbances** – low blood pressure, constipation
- **Late Features**
  - Excessive sleepiness
  - Depression and anxiety
  - Dementia

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Advances in Motor Treatments

- **What is the current state of the art?**
- **What new treatments for motor symptoms are on the horizon?**
  - Levodopa delivery strategies
  - Next Generation DBS

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Discovery of Levodopa

Rabbits that became immobile (akinetic) after being reserpinized (upper panel) and then were restored to good mobility after being treated with l-dopa (Figure from Carlsson's Nobel Lecture.

The New England Journal of Medicine

Volume 280 FEBRUARY 13, 1969 Number 7

MODIFICATION OF PARKINSONISM – CHRONIC TREATMENT WITH L-DOPA*

GEORGE C. COTZIAS, M.D., PAUL S. PAPAVASILIOU, M.D., AND ROSEMARY GELLENE, M.D.

Abstract Slowly increasing oral doses of l-3,4-dihydroxyphenylalanine (l-dopa) induced at least partial improvement of some manifestations in a series of 28 patients with Parkinsonism. Improvement of performance was graded as modest in four, moderate in four, marked in 10 and dramatic in 10. This was usually sustained for periods up to two years. Evidence of toxicity was signaled by few of the variables monitored. Mental effects included enhanced interest, improved memory, transitory sleeplessness and nervousness. Nausea and vomiting were largely circumvented by slowing of the increases of the daily dose. A peripheral dopa-decarboxylase inhibitor diminished the therapeutic dose of l-dopa required and eliminated anorexia and nausea in one case. Neurologic side effects consisted of involuntary movements ranging from fleeting to severe.

Dr. George C. Cotzias
Brookhaven Lab, 1970

Standard Dopaminergic Treatments for PD

- **Levodopa/carbidopa (Sinemet®)**
- **Pramipexole (Mirapex®)**
- **Ropinerole (Requip®)**
- **Rotigitine (Neupro®)**
- **Apomorphine (Apokyn®)**
- **Others that affect dopamine indirectly:**
  - Rasagiline (Azilect®)
  - Entacapone (Comtan®, Stalevo®)

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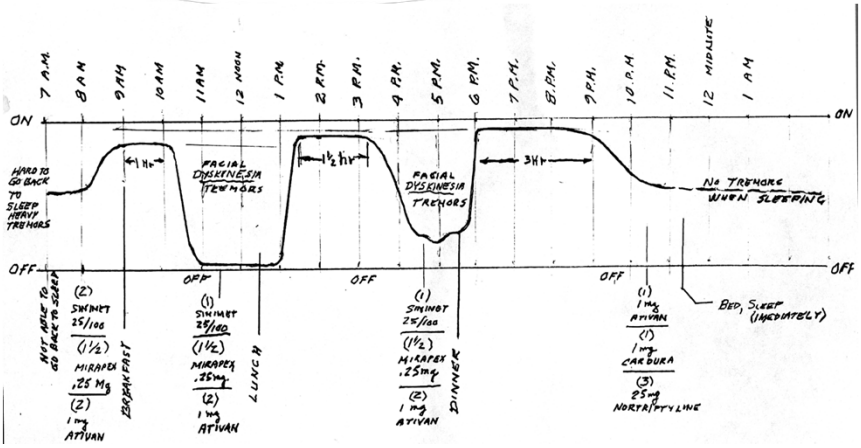
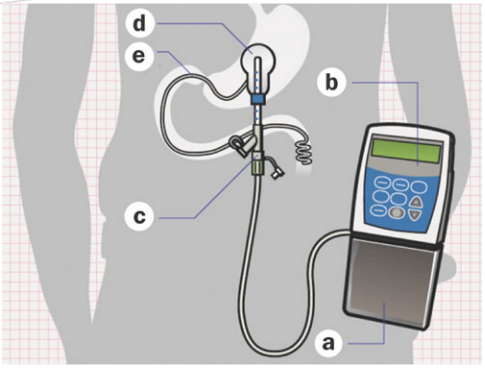
Motor Complications of Levodopa



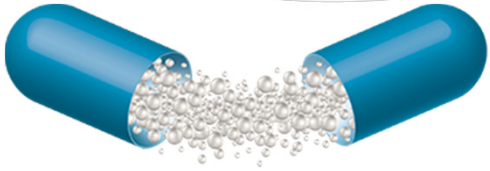
Duopa®: Carbidopa/Levodopa Gel

- Carbidopa/Levodopa in a gel form, infused in to the intestines using a pump.
- FDA approved
- Intended for patients with wearing off and fluctuations



Richards, L. (2009) Intrajejunal duodopa improves nonmotor symptoms. *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2009.84

Rytary®



Each capsule contains both:
- Immediate-release beads.
- Extended-release beads.[2]

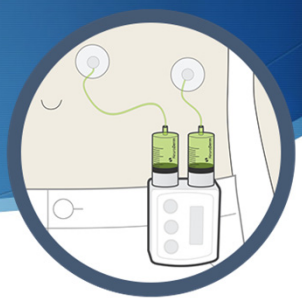
- Controlled release levodopa/carbidopa
- FDA Approved
- Reduces wearing off in advanced PD
- Side effects similar to levodopa/carbidopa

Inhaled Levodopa CVT-301

- **Experimental treatment for OFF periods in people with Parkinson's disease taking an oral carbidopa/levodopa regimen.**
- **February 9, 2017: Acorda announced Phase 3 results, showing a statistically significant improvement in motor function in patients experiencing OFF periods.**
- **Cough was the most common adverse event, reported by approximately 15% of subjects who received CVT-301.**
- **They plan to file a New Drug Application with the U.S. Food and Drug Administration in the second quarter of 2017**

15 Acorda press release 02/14/2017

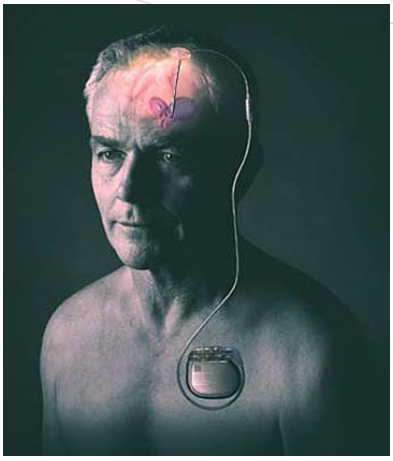
Subcutaneous Levodopa Infusion



- **A continuous levodopa therapy**
- **Trial 006 demonstrated that the trial successfully met its primary, key secondary and additional secondary endpoints.**
- **From 5.5 hours at baseline, the OFF-time was reduced by 2.8 hours (p equals 0.004).**
- **42% of patients had a complete reduction in OFF-time to zero hours**

16 Neuroderm Press Release March 01, 2017

Deep Brain Stimulation



Mahlon R. DeLong
Emory University
School of Medicine

Alim Louis Benabid
Joseph Fourier University

2014 Lasker Foundation
DeBakey Clinical Medical Research Award

Next Generation DBS

- **New device technologies**
- **Better programming**

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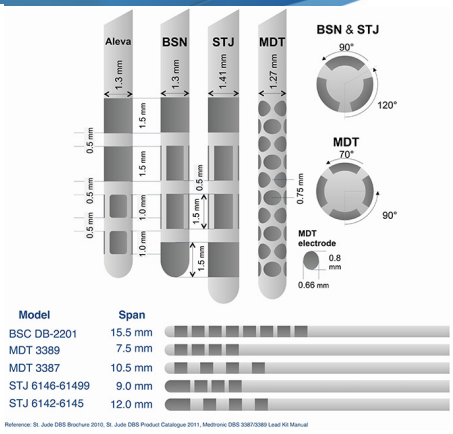
St. Jude DBS Device

FDA Approved October 2016



19 Front. Neurosci., 06 April 2016

BRAIN Initiative DBS Projects: $20M in New Research Funding

BRAIN INITIATIVE — BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES

NIH National Institutes of Health

- **Closing the Loop on Tremor: A Responsive Deep Brain Stimulator for the Treatment of Essential Tremor (Dr. Kelly Foote, Univ. Florida)**
- **Noninvasive Biomarkers to Advance Emerging DBS Electrode Technologies in Parkinson's Disease (Dr. Harrison Walker, UAB)**
- **Closed loop deep brain stimulation for Parkinson's disease (Dr. Philip Starr, UCSF)**

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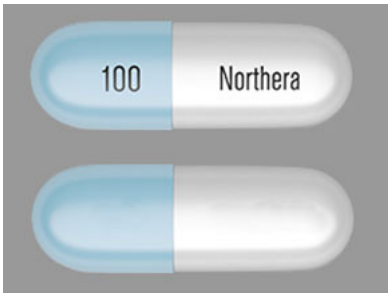
New Treatments – Non-motor Therapies

- Northera® - droxidopa
- Nuplazid® - pimvanserin

Northera® (droxidopa)

- Approved for treatment of orthostatic hypotension in Parkinson disease
- One of several treatments for low blood pressure and dizziness in PD



Nuplazid® (pimvanserin)

- Atypical antipsychotic
- Inverse agonist of the serotonin 5-HT2A receptor
- Treatment of hallucinations and delusions associated with Parkinson's disease psychosis
- Warning against use in dementia-related psychosis

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What is coming soon?

Some Highlights From Clinicaltrials.gov

- **More ways to deliver dopamine**
  - Levodopa "accordion pill"
  - Apomorphine – infusion, nasal, "strips"
- **Treatments for wearing off and dyskinesia**
  - Sustained release amantidine
  - A2a antagonists – Istradefyline, Tozadenant
- **Exercise**
  - What is the right "prescription" for exercise?

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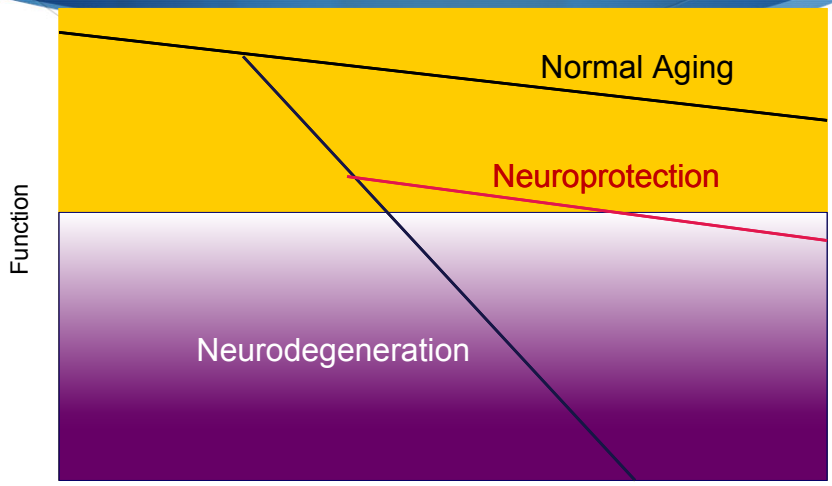
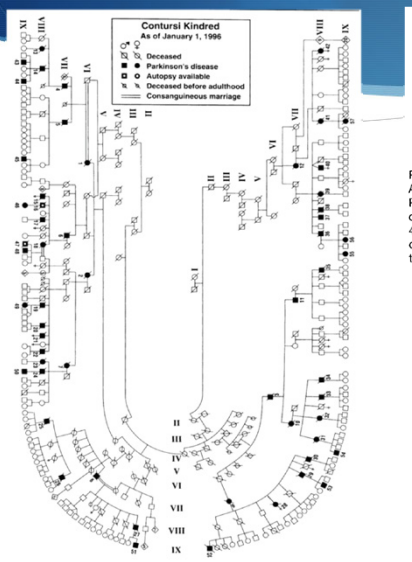
Neuroprotective Therapies



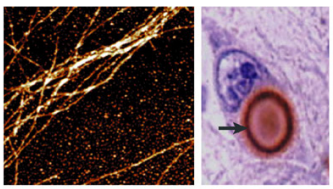
Alpha-synuclein, a Gene for PD



Mapping of a Gene for Parkinson's Disease to Chromosome 4q21–q23

Mihael H. Polymeropoulos,* Joseph J. Higgins, Lawrence I. Golbe, William G. Johnson, Susan E. Ide, Giuseppe Di Iorio, Giuseppe Sanges, Edward S. Stenroos, Lana T. Pho, Alejandro A. Schaffer, Alice M. Lazzarini, Robert L. Nussbaum, Roger C. Duvoisin

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting approximately 1 percent of the population over age 50. Recent studies have confirmed significant familial aggregation of PD and a large number of large multicase families have been documented. Genetic markers on chromosome 4q21–q23 were found to be linked to the PD phenotype in a large kindred with autosomal dominant PD, with a $Z_{max} = 6.00$ for marker *D4S2380*. This finding will facilitate identification of the gene and research on the pathogenesis of PD.



Science; Nov 15, 1996; 274, 5290

Anti-Synuclein Therapies

- Goal it to reduce alpha-synuclein in the brain
- Potentially a treatment to slow the disease, and prevent both motor and non-motor symptoms
- When should be use them – what is the right stage of disease?

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Anti-synuclein: Immunotherapies

- **Antibodies to synuclein, with goal of reducing it in brain and blood**
- **Trials will focus on early clinical PD**
- **Two trials underway or recently completed:**

22	Recruiting	Single-Ascending Dose Study of BIIB054 in Healthy Participants and Early Parkinson's Disease **Conditions:** Parkinson's Disease; Healthy **Interventions:** Drug: BIIB054; Drug: Placebo
30	Completed	AFF008E: Observational Phase 1b Follow-up Extension Study for Patients With Parkinson's Disease After Immunization With AFFITOPE® PD01A **Condition:** Parkinson's Disease **Intervention:**

28 Clinicaltrials.gov

Anti-Synuclein Therapies: The Next Wave

- **Reducing synuclein production**
  - Antisense oligonucleotides
- **Enhancing synuclein clearance**
  - Autophagy enhancers (nilotinib, others)
- **Reducing synuclein aggregation**
  - Antibodies
  - Small molecules

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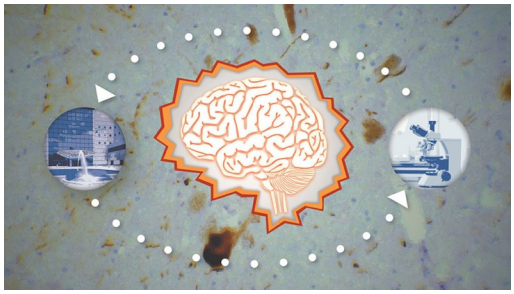
PD and Inflammation: *Turning Down the Heat*

- Too much synuclein in the brain activates the immune system
- Immune cells and antibodies damage dopamine neurons
- Would blocking inflammation slow the progress of PD?



Summary

- **We have important new treatments for both motor and non-motor symptoms**
  - Levodopa delivery
  - Next generation DBS
  - Blood pressure symptoms, hallucinations
- **Soon, we will see better treatments for PD symptoms**
  - More effective ways to deliver dopaminergic drugs
  - Treatments for non-motor symptoms
- **The "cutting edge" of research is the search for neuroprotection**
  - Anti-synuclein strategies are at the forefront today
  - Anti-inflammatory approaches not far behind

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Question & Answer

David G. Standaert, MD, PhD
John N. Whitaker Professor and Chair of Neurology
The University of Alabama Birmingham School of Medicine
Chair, APDA Scientific Advisory Board

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Closing Remarks

Stephanie Paul
Vice President Development and Marketing
American Parkinson Disease Association

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For additional information, answers to your questions, or resources

Please visit our website
www.apdaparkinson.org

Or call us
1-800-223-2732

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