



Parkinson's Disease

Past-Present-Future

1817-2017-2217

Stephen L. Lee MD PhD
Medical Director of Movement Disorders Center
Assistant Professor of Neurology
Dartmouth Hitchcock Medical Center



Financial Disclosures

Employed by Dartmouth-Hitchcock



200 years ago...

AN
ESSAY
ON THE
SHAKING PALSY.

BY
JAMES PARKINSON.
FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS.

LONDON:
PRINTED BY WATTS, TAYLOR, AND WOODWARD,
ST. MARTIN'S LANE.
FOR GREENWOOD, REELEY, AND JONES,
PATERNOSTER ROW.
1817.

To divert blood and inflammatory pressure away from the brain and spinal cord...

1. Blood should be taken from the upper part of the neck.
2. Apply vesicalants to the same part to obtain a purulent discharge.
3. Blister again whenever pus is not secreted in sufficient quantities.
4. If this is not effective make incisions 1-5 inches in length on each side of the vertebral column in its superior part. Keep open with proper caustic or cork.
5. Employment of internal medicines are scarcely warrantable but a trial of mercury might be used.
6. Purge the bowel because it can affect the spinal cord at a distance.

Chapter V. Considerations and Respecting the Means of a Cure. Essay on the Shaking Palsy. James Parkinson. 1817.



Jean-Martin Charcot, 1860-90s

- Anticholinergics (Hyoscyamine)
- Bella-donna alkaloids
- Rest/relaxation
- Vibration therapy

Charcot's Vibration Therapy...



Vibration Therapy for Parkinson's Disease: Charcot's Studies Revisited



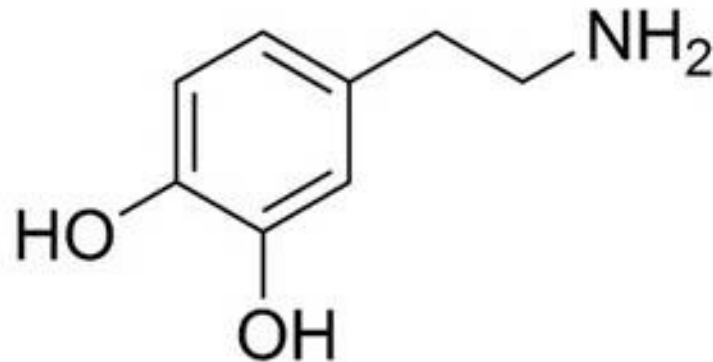
“Vibration Therapy for Parkinson's Disease: Charcot's Studies Revisited,”
by A.S. Kapur, G.T. Stebbins, and C.G. Goetz. *Journal of Parkinson's Disease*,
2(2012) 23-27. DOI: 10.3233/JPD-2012-12079. Published by IOS Press.



Present: Modern Era 1910-2017

Dopamine

1910



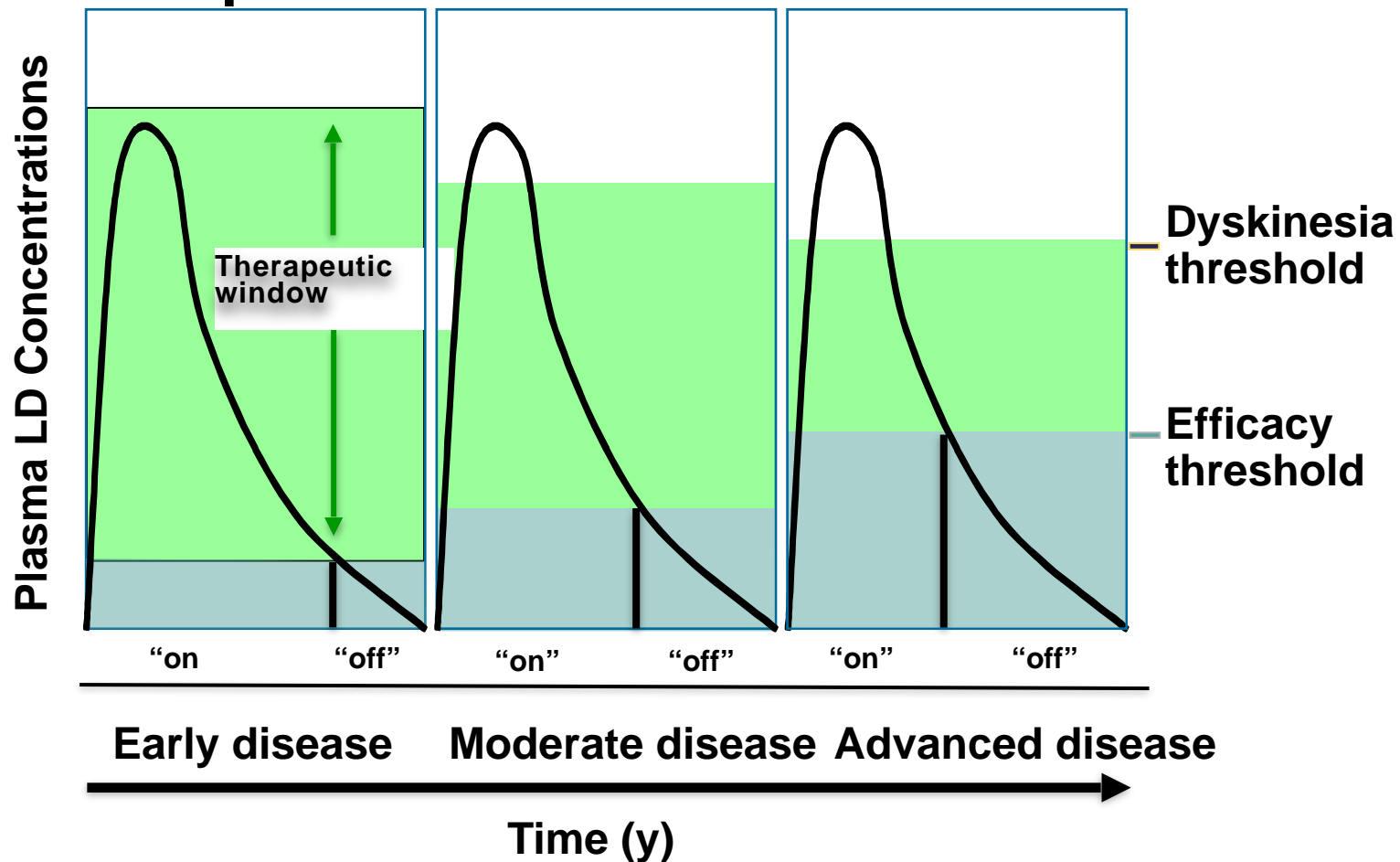
- First synthesized by Barger and Ewens
- P. Holtz discovered **dopa decarboxylase** and documented that **levodopa** was synthesized to **dopamine** through its action

Dopamine

1950's and 60's

- Discovered in the striatum, found to be important for movement
- A series of PD brains examined post-mortem and found to have striatal dopamine depletion
- Birkmeyer and Hornykiewicz injected Levodopa IV for the 1st time in **1961**, “bed-ridden patients who were unable to sit, patients could not stand up when seated, and patients who when standing could not start walking, performed all these activities with ease after L-dopa. They walked around with normal associated movements and they could even run and jump. The voiceless, aphonic speech, blurred by pallilalia and unclear articulation, became forceful and clear as in a normal person”.

Levodopa over time...



Nat Clin Pract Neurol., Olanow CW, Obeso JA, Stocchi F. Drug insight: Continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Nat Clin Pract Neurol.* 2006;2:382-392.



PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's



Dartmouth-
Hitchcock



Dartmouth
GEISEL SCHOOL OF
MEDICINE



PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s



PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s



PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s



PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)

PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)
- Ropinirole and Pramipexole (dopamine agonists) 1997

PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)
- Ropinirole and Pramipexole (dopamine agonists) 1997
- Tolcapone and Entacapone (COMT inhibitors) 1998

PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)
- Ropinirole and Pramipexole (dopamine agonists) 1997
- Tolcapone and Entacapone (COMT inhibitors) 1998
- Stalevo (Carbidopa/Levodopa/Entacapone) 2003



PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)
- Ropinirole and Pramipexole (dopamine agonists) 1997
- Tolcapone and Entacapone (COMT inhibitors) 1998
- Stalevo (Carbidopa/Levodopa/Entacapone) 2003
- Apokyn (apomorphine, injectable), 2004

PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)
- Ropinirole and Pramipexole (dopamine agonists) 1997
- Tolcapone and Entacapone (COMT inhibitors) 1998
- Stalevo (Carbidopa/Levodopa/Entacapone) 2003
- Apokyn (apomorphine, injectable), 2004
- Rasagiline (MAO-B inhibitor), 2006

PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)
- Ropinirole and Pramipexole (dopamine agonists) 1997
- Tolcapone and Entacapone (COMT inhibitors) 1998
- Stalevo (Carbidopa/Levodopa/Entacapone) 2003
- Apokyn (apomorphine, injectable), 2004
- Rasagiline (MAO-B inhibitor), 2006
- Neupro (rotigotine, patch), 2007/2010

PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)
- Ropinirole and Pramipexole (dopamine agonists) 1997
- Tolcapone and Entacapone (COMT inhibitors) 1998
- Stalevo (Carbidopa/Levodopa/Entacapone) 2003
- Apokyn (apomorphine, injectable), 2004
- Rasagiline (MAO-B inhibitor), 2006
- Rotigotine Patch, in 2007/2010
- Requip XL, 2008

PD Medication Timeline...

- Amantadine (anti-flu, re-uptake of striatal dopamine) 1960's
- Selegiline (MAO-B inhibitor) 1970s
- Bromocriptine (1st Dopamine agonist) 1970s
- Pergolide (dopamine agonist) 1980s
- DBS FDA approved for Parkinson's disease in 1997 (STN)
- Ropinirole and Pramipexole (dopamine agonists) 1997
- Tolcapone and Entacapone (COMT inhibitors) 1998
- Stalevo (Carbidopa/Levodopa/Entacapone) 2003
- Apokyn (apomorphine, injectable), 2004
- Rasagiline (MAO-B inhibitor), 2006
- Rotigotine Patch, in 2007/2010
- Requip XL, 2008
- Mirapex ER, 2010

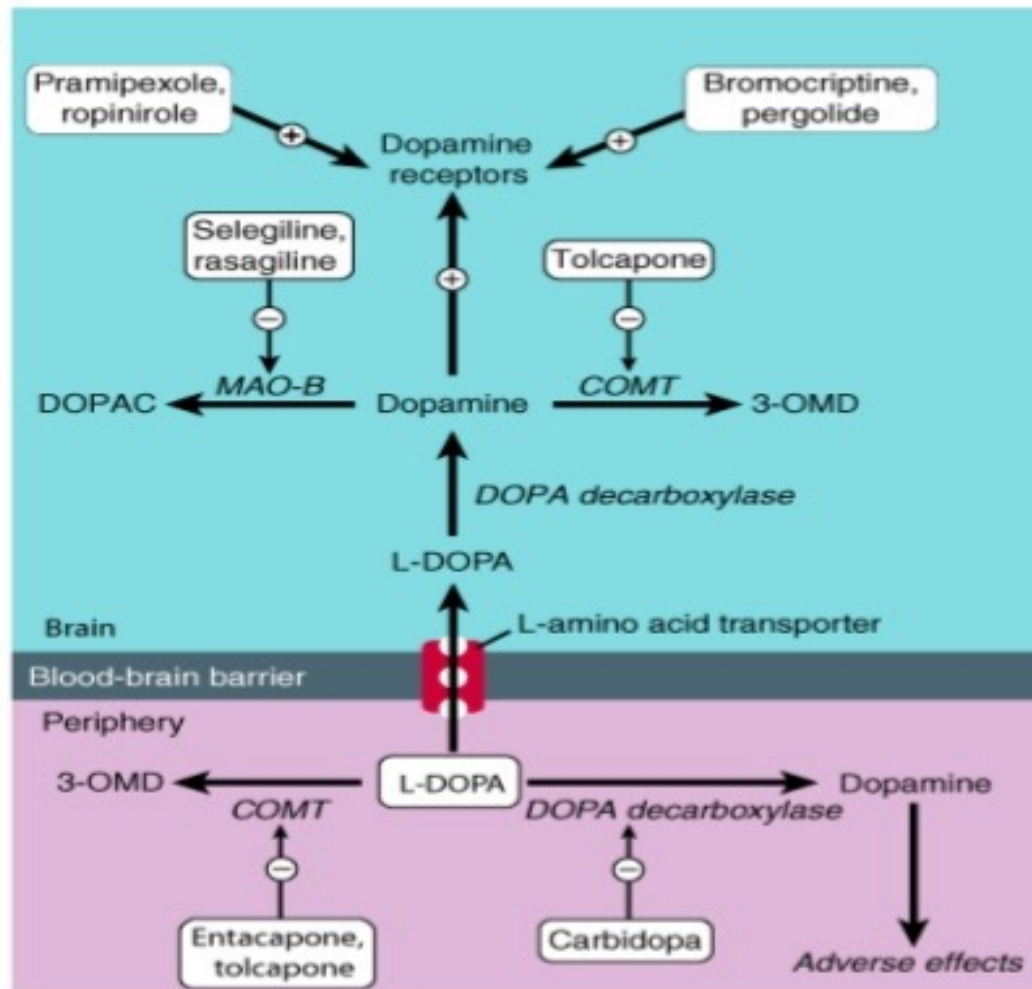


PD medication management goals

- Keep “on” time even
- Minimize motor fluctuations
- Minimize “off” times

*Keep dopamine levels **even**...*

MOA of PD drugs...



2 New PD Drugs in 2015

- Rytary (Extended Release Carbidopa/Levodopa)

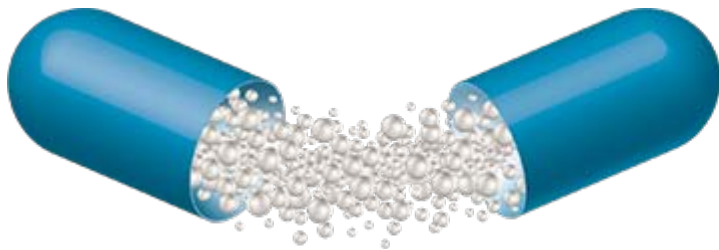


- Duodopa (Carbidopa/Levodopa Enteral Suspension)



Rytary – Extended Release Carbidopa/Levodopa

- Micro-encapsulated bead system – IR and ER beads
- Multiple doses available
- Dosed typically 3 times daily (every 6 hours)



Each capsule contains both:

- Immediate-release beads.
- Extended-release beads.²

Duodopa: Carbidopa/Levodopa Enteral Suspension

- Via PEG- J tube



DBS vs Duopa

- 40 patients: either STN DBS or Duopa therapy
- Similar UPDRS II, UPDRS III, and UPDRS IV scores
- Similar “on”/ “off” times
- Similar efficacy
- However – *slightly* MORE procedure related complications with Duopa (PEG-J)

Comparison of subthalamic nucleus deep brain stimulation and Duodopa in the treatment of advanced Parkinson's disease. Merola, et al. Mov. Disorders. 2011 Mar;26(4):664-70

The patients....



Dartmouth-
Hitchcock



Dartmouth
GEISEL SCHOOL OF
MEDICINE



2017 Drug Therapies for Motor Fluctuations

More “on” Time

- **Safinamide (*Xadago*)**– Unique molecule, dual Mechanism of action. Both MAO-B inhibitor/ inhibits excess glutamate (decrease in dyskinesia, increase in “on time”) – Approved by FDA

Neurosurgery for PD

- 1953: Irving Cooper: accidental ligation of the anterior choroidal a.
- 1950-1970s: ablative surgery (thalamotomy and pallidotomy) were performed for severe forms of the disease
- 1968 L-Dopa first used
- 1980s Deep brain stimulation developed
- 1987 Deep brain stimulation therapy applied
- 1997 First FDA approval for tremor
- 2002 FDA approval for DBS for PD
- 2003 FDA approves DBS for dystonia
- 2016 FDA approves DBS for Recent onset of Motor Complications
- 2016 FDA approves Infinity DBS (St. Jude/Abbott)

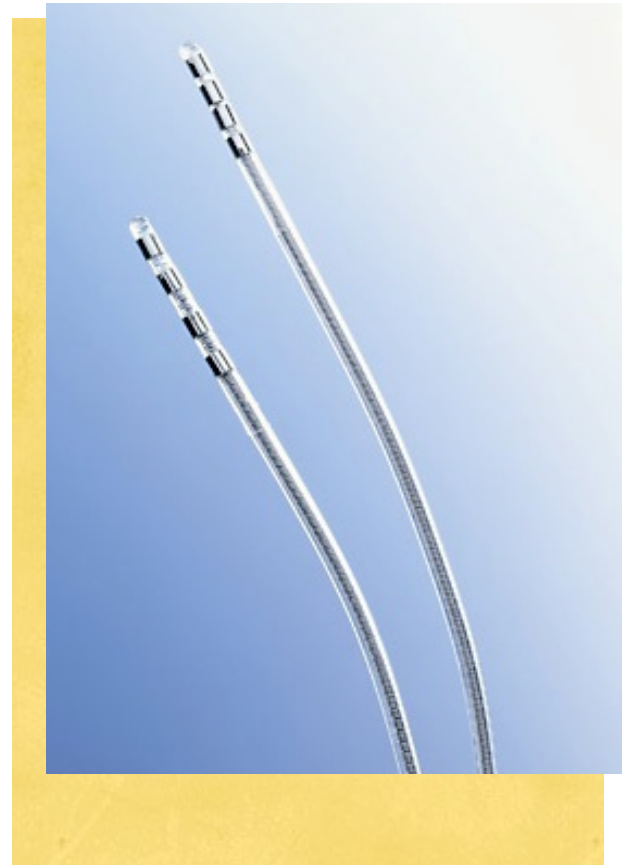


ACTIVA[®]

deep brain stimulation

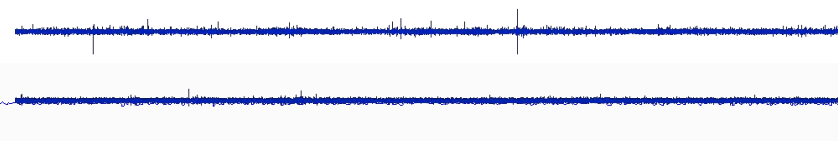
Surgical Technique: DBS Lead Placement

- Leads placed in motor territory of nucleus
- Leads have four electrodes
- Multiple electrode configurations possible during post-operative programming

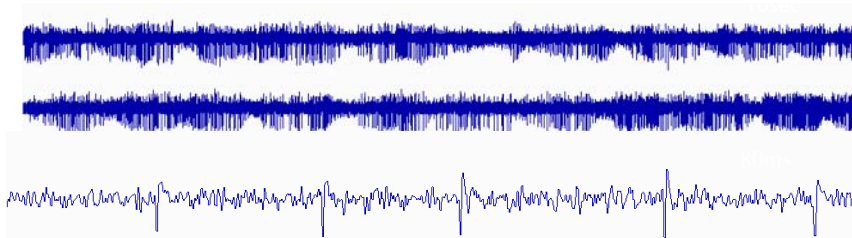


Surgical Technique: Microelectrode Recording

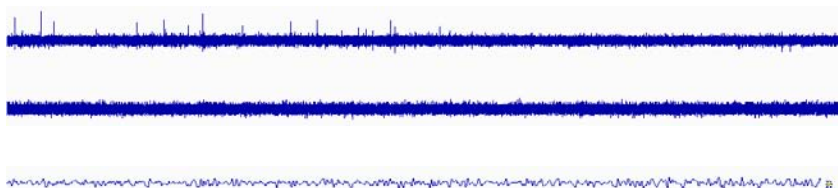
Border



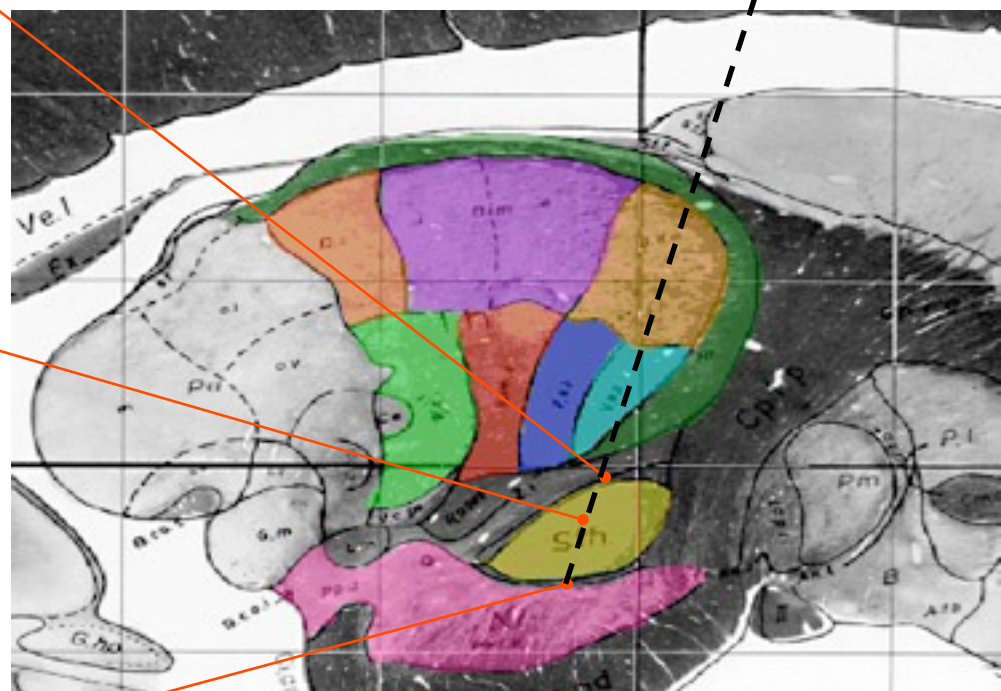
STN



Border/SN



Sagittal Section Through the Thalamus

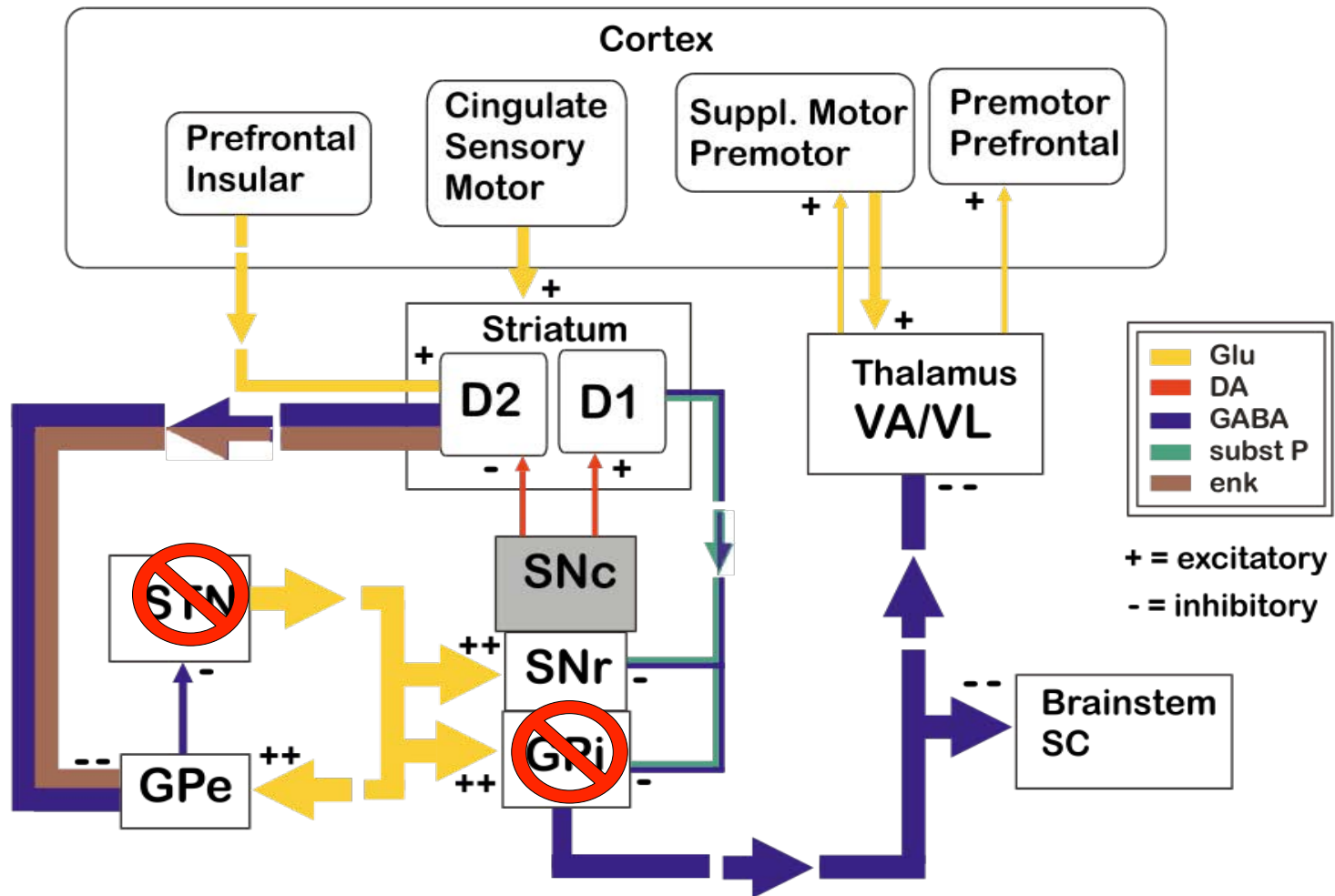




Surgical Technique: Neurostimulator Placement

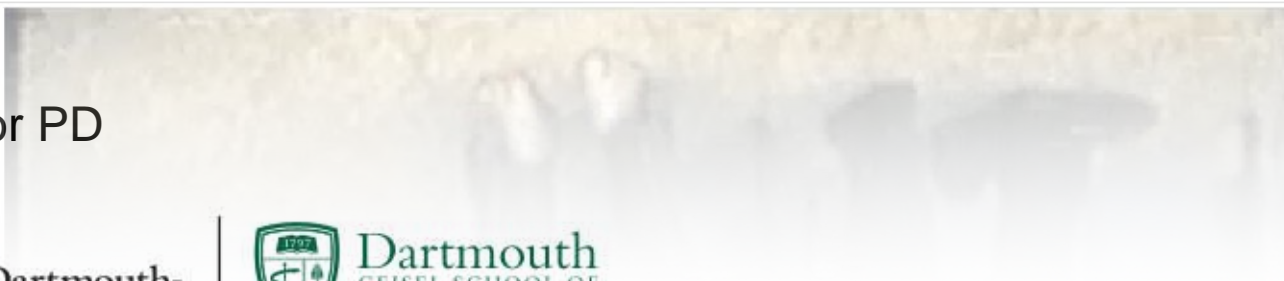
- Can be done immediately or days/weeks later
- Typically placed below clavicle
- Connected to lead using extension

DIRECT AND INDIRECT PATHWAYS IN PARKINSON'S DISEASE (CLICK TO EXIT)



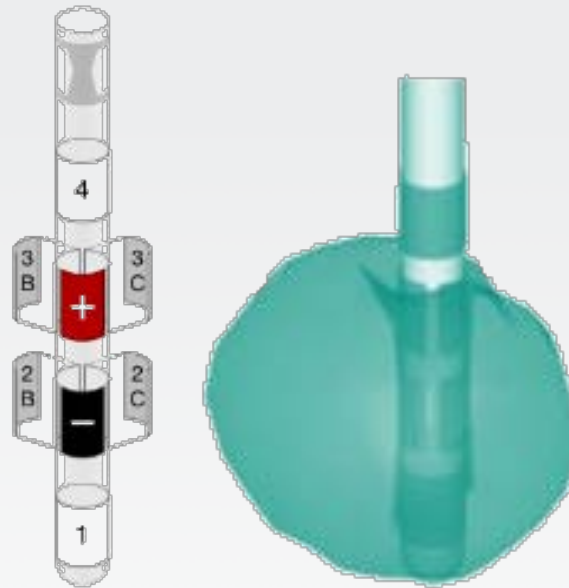


DBS for PD



DIRECTIONAL LEAD FOR ENHANCED CONTROL, DURABILITY, AND PATIENT COMFORT^{1,2}

Segmented electrode lead designed to **precisely steer current towards desired structural areas** to help **maximize patient outcomes** and **reduce side effects**.



Directional lead for the
St. Jude Medical Infinity™ DBS system



Future Drug Therapies for PD symptoms

More “on” Time

- **Opicapone** – 3rd generation COMT inhibitor. Phase III trial completed. Superior to Entacapone and only once daily. Reduced off time.



Future: Beyond 2017



Dartmouth-
Hitchcock



Dartmouth
GEISEL SCHOOL OF
MEDICINE



Parkinson's disease (wikipedia entry, ca 2217)

Parkinson's disease afflicted several million people over the last two centuries, having been effectively eradicated thanks to work by ____ and ____ who collaborated to show how to prevent the disease from happening.

Advances in treatment also meant that those who suffered from it had the disease eventually stopped and reversed.

(Reference: ____)

Disease Modification

Slowing/stopping Clinical Progression is the Ultimate Goal of Parkinson's Therapy!!





Neuroprotection Pipeline: disease modification

Here at Dartmouth-Hitchcock:

**Isradapine: STEADY PD III trial: NIH sponsored study to show
disease modification**

- **Calcium channel blockers associated with a reduced risk of developing PD**
- **Isradapine has been shown to protect SNpc neurons from 6-OHDA toxicity in a rodent model**
- **Ongoing for 36 months.**
- **Double blinded, placebo controlled study.**



Neuroprotection Pipeline: disease modification

SURE-PD III (UVM, and other US sites) (Safety of Urate Elevate in PD)

- **Inosine** → raises serum urate levels
- Urate possess antioxidant properties; elevation of urate levels in rodent models can protect SNpc dopaminergic neurons from 6-OHDA toxicity
- Epidemiological studies: higher urate levels are associated with reduced risk of developing PD

Neuroprotection Pipeline: disease modification

Immunization against α -synuclein

- α -synuclein is an abundant protein in the brain and blood, normal physiologic functions poorly understood
- ? Which α -Syn aggregate species are most toxic to the neurons in PD
- Develop an immunization (passive/active immunity) against those toxic aggregates

Neuroprotection Pipeline: disease modification

Immunization against α -synuclein

4 Clinical Trials underway currently, clinicaltrials.gov:

- NCT02216188 (active immunization)
- NCT01885494 (active immunization)
- NCT02267434 (active immunization)
- NCT02157714 (passive immunization)



Neuroprotection Pipeline:
disease modification

ON GOING

Glial cell line derived neurotrophic Factor (GDNF)

- **NIH sponsored**
- **Direct infusion into the putamen caused neutralizing antibodies in humans**
- **Trial still underway/NIH-NINDS: NCT01621581 → using a gene therapy vector (AAV2)**



Neuroprotection Pipeline:
disease modification

NO TRIALS YET

Leucine Rich repeat Kinase 2 Inhibitors (LRRK2 inhibitors)

- May slow degenerative process
- May play a pivotal role for the future
- Further investigation needed

Neuroprotection Pipeline: disease modification

COMPLETED

- Coffee → associated with a reduced risk of PD (according to epidemiological studies), also may have symptomatic benefits. Being investigated in a large study currently. Patients taking either 200-400 mg/d of caffeine had better UPDRS scores on pilot study.
 - Extension study to be done
 - Delayed start trial to be done to show neuro-protection
- Nicotine → Epidemiological studies identified tobacco smoking to be associated with reduced risk of developing PD
 - Phase II RCT investigating TD nicotine currently recruiting subjects

Future Drug Therapies for Motor Fluctuations

RECRUITING

For “off periods”

- **Inhaled-Levodopa (CVT-301)** Acorda Pharmaceuticals: in the treatment of “off” episodes in PD. Phase III is now underway. The medication will be inhaled with an actuator, for rapid delivery
- **Inhaled-Apomorphine (VR-040)** – phase III underway, Efficacy and safety of phase II trial were very successful
- **Sublingual Apomorphine (APL-130277)** Cynapsus – phase III currently underway. Another rescue therapy for off periods.



Future Drug Therapies for Motor Fluctuations

Here at Dartmouth-Hitchcock Medical Center, 2016-2017:

RECRUITING

A Phase III, Multicenter, Randomized, Double-Blind, Double-Dummy, Active- Controlled Study Comparing the Efficacy and Safety of Gastric Retentive, Controlled Release Accordion Pill™ Carbidopa/Levodopa (AP-CD/LD) to Immediate Release CD/LD in Fluctuating Parkinson's Disease Patients

- **32 wk study, for fluctuating PD patients currently on Levodopa with approximately 2.5 hours of “off time”**

Future Drug Therapies for Motor Fluctuations

Treatment of Dyskinesia

- **Amantadine ER (*Nurelin*)**– once daily, glutamate NMDA antagonist (anti-dyskinetic effect) – also increased “on” time, and did not cause insomnia as the immediate release formula did.
- **Eltoprazine** – selective partial agonist at the 5-HT_{1A}/HT_{1B} receptors with antidyskinetic activity, phase II trial underway.
- **Caffeine** – adenosine receptor antagonist; CALM PD study: consumption higher than 12 oz/day associated with less frequent dyskinesia as compared with consumers of less than 4 oz/day





Many other new drugs/Research being done

For **psychosis** (Pimavanserin),

Orthostatic hypotension (Droxidopa – Clinical trial approved by IRB here at DHMC, Mary Feldman, PI, Jeff Cohen, MD)

New meds for **dementia** being investigated,

Gene therapy,

Research into **balance/gait** (Dr. Lee's visual adaptation study underway here at DHMC),

More **targets** for **DBS surgery**

Neuroinflammation (translational study “Inflammasomes in PD” sponsored by Michael J Fox Foundation, Matt Havrda, PhD, PI, Steve Lee, Mary Feldman).

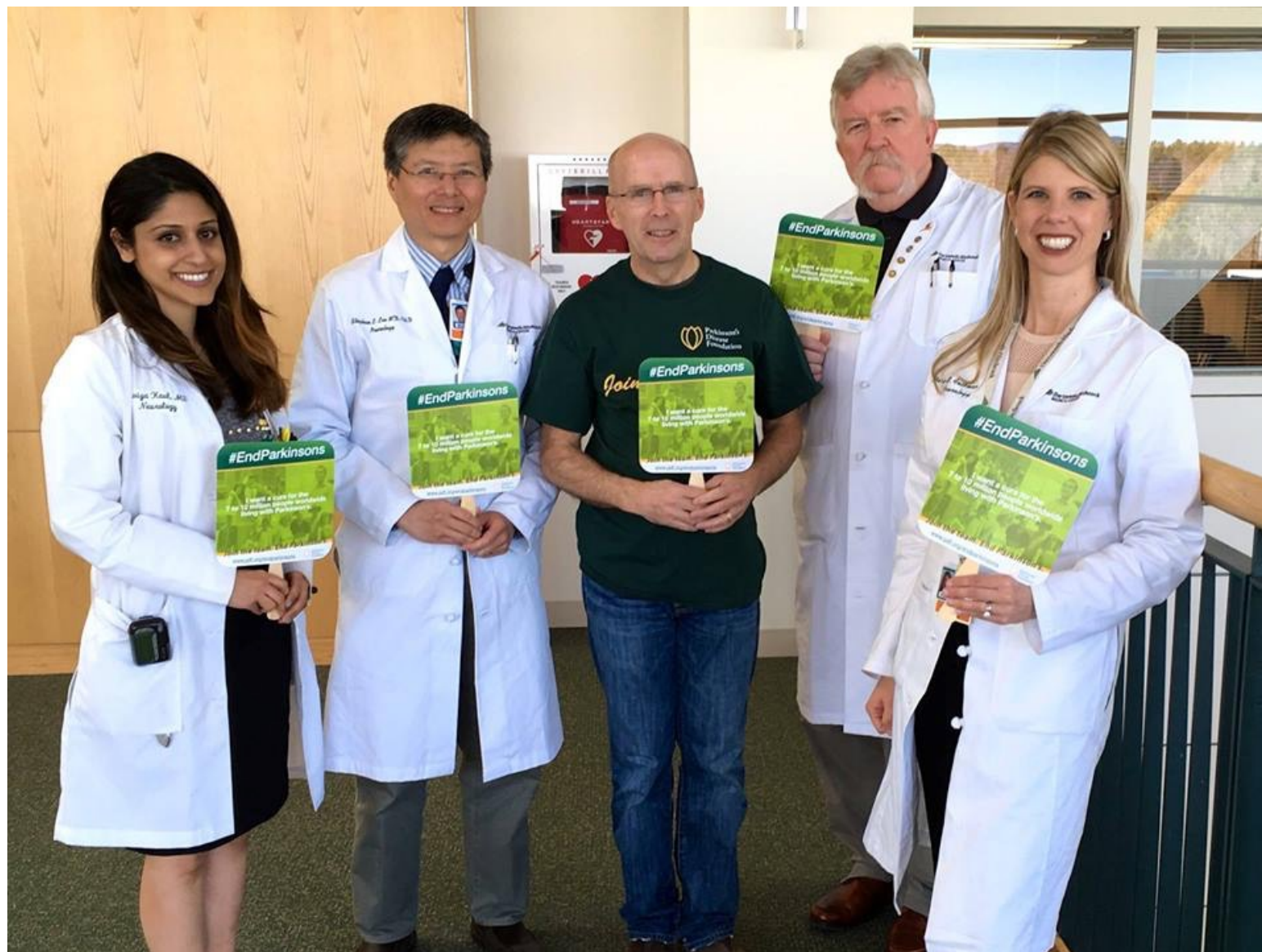
DHMC Parkinson's group



Dartmouth-
Hitchcock



Dartmouth
GEISEL SCHOOL OF
MEDICINE



Questions?



Dartmouth-
Hitchcock



Dartmouth
GEISEL SCHOOL OF
MEDICINE