ADVANCEMENTS IN THE TREATMENT OF PARKINSON’S DISEASE

Neurorestoration and Beyond
WHAT IS PARKINSON’S?

There is NO TEST and no PROGRESSION MARKER

NO CURE, MEDICATION ONLY HELPS WITH SYMPTOMS

PARKINSON’S DISEASE IS CAUSED BY THE DEATH OF DOPAMINE CELLS.

60 TO 80% OF THESE CELLS ARE ALREADY LOST BY THE TIME MOTOR SYMPTOMS APPEAR.

1/100 OVER AGE OF 60

60,000 NEW

1M/US

5M/ WORLD
WHAT CAUSE PARKINSON’S DISEASE?

PARKINSON’S DISEASE IS CAUSED BY A DECREASE IN DOPAMINE PRODUCTION IN THE BRAIN

[Diagram showing normal neuron and neuron affected by Parkinson's disease with dopamine and dopamine receptors]
WHAT HAPPENS IF YOU HAVE REDUCED DOPAMINE?

- **Motor and Non-motor Symptoms**
  - Systems which function inappropriately due to reduction in Dopamine or one of its byproducts

- **Motor Symptoms**
  - Resting tremor
  - Tremor with position
  - Bradykinesia (slowness)
  - Rigidity (stiffness)
  - Slow walking, shuffle, reduced arm swing
  - Balance issues
  - Reduced facial expression (flat affect)
  - Speech changes (hypophonia)
**Can present years before diagnosis**

- Loss of sense of smell
- Constipation
- Talking in sleep or acting out dreams
- Anxiety/Depression
- Bladder issues
- Excessive saliva/drooling
- Vision changes
- Problems sweating
- Lightheadedness/Dizziness on standing
- Fatigue
- Skin problems
- Cognitive changes
The symptoms of Parkinson’s disease vary from person to person, but may include both motor and non-motor symptoms.

**Before Diagnosis**
- Early:
  - Slowed movement
  - Rigidity
  - Tremor

**After Diagnosis**
- Advanced/Late:
  - Difficulties speaking
  - Difficulties with posture
  - Freezing of gait
  - Falls

- Non-motor:
  - Constipation
  - REM sleep behavior disorder
  - Reduced ability to smell
  - Depression
  - Pain
  - Fatigue
  - Urinary symptoms
  - Orthostatic hypotension
  - Dementia

**Degree of Disability vs. Time (years)**
WHY DOES PD CHANGE OVER TIME?

Current debate - the disease itself AND medications used?

![Graph showing change in levodopa response over time for Early PD, Moderate PD, and Advanced PD.](image1)

![Graph showing plasma dopa levels over time.](image2)

*Source: Schapira et al, 2009*
WHY DOES PD CHANGE OVER TIME?

Classic carbidopa/levodopa

- ELLDOPA trial 16.5% of patients randomized to 600 mg of LD daily developed dyskinesias after only 9 months of treatment versus 2.3% among those on 300 mg (2004)
- Worsening motor complications with doses ≥ 600mg per day at 6 months and 6 years (2005)
- STRIDE-PD trial showed increased motor fluctuations and dyskinesia ≥ 500mg per day at 6 years (2013)

Combination of disease progression and pulsatile medication dosing impacts the number of dopamine receptors present among other things.

Result = Worsening on-off fluctuations throughout the day
# Approach to Therapy

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PARKINSON’S DISEASE MEDICINES WORK TO INCREASE DOPAMINE OR ACT LIKE DOPAMINE IN THE BRAIN

COMT inhibitors slow the breakdown of levodopa
Levodopa replaces dopamine
Dopamine agonists mimic dopamine
MAO-B inhibitors slow the breakdown of existing dopamine

Synapse (space between neurons)

COMT = catechol-O-methyltransferase.
MAO-B = monoamine oxidase-B.
Kalia LV et al. Lancet. 2015;386:896–912
EXPANDED TOOLBOX UP UNTIL 8 YEARS AGO

- Dopamine Agonist
  - Neupro® (Rotigotine Transdermal System)
  - REQUIP® (ropinirole HCl)
  - Mirapex®

- Carbidopa/Levodopa formulation

- MAOB inhibitor
  - AZILECT® (rasagiline tablets)

- COMT inhibitor
  - Stalevo®
  - COMTan® (entacapone) tablets
Rytary

- New formulation to deliver Carbidopa-Levodopa.
- Can last from 5 to 8 hours compared to 2 to 3 hours for Sinemet.
  - 1 to 2 hours less off time, 2 hours more on time


Safinamide (Xadago)

- Reversibly inhibits the MAO-B enzyme
- Boosts natural dopamine and potentiates artificial dopamine

- 1x daily

- Similarity to rasagiline (Azilect) which is now generic but still expensive to some

NEW MAO-B INHIBITOR, AUGMENTING THE SYSTEM

Reduction in UPDRS III scores over 2 years:

- XADAGO 50 mg/day: -5.0 ± 3.3 (n=189)
- XADAGO 100 mg/day: -6.1 ± 3.5 (n=180)
- Placebo: -3.9 ± 3.6 (n=175)

Baseline Score: XADAGO 50 mg: 27.3
XADAGO 100 mg: 28.3
Placebo: 28.7

STUDY 016 (18-MONTH EXTENSION OF STUDY 1)
Apokyn (apomorphine injection)

- Rapid onset Dopamine Agonist via injection
- For different types of OFF episodes:
  - Rapid off, wearing off
  - Dose failure / unexpected off
  - Delayed on
  - First AM symptoms or exercise intolerance
- Achieve ON within 10-20 minutes
Inbrija (levodopa inhalation powder)

- Rapid onset levodopa through inhaler
- For different types of OFF episodes:
  - Rapid off, wearing off
  - Dose failure / unexpected off
  - Delayed on
  - First AM symptoms or exercise intolerance
- Achieve ON within 10 minutes, can take up to 5x daily

**UPDRS Part III Score Change From 0-60 Minutes Postdose at Week 12**

![Graph showing INBRIJA's effectiveness compared to placebo over time](chart.png)

Primary endpoint $P=0.009$
Amantadine ER (Gocovri)

- 1x daily amantadine
- First “FDA approved” therapy for dyskinesia
  - Classic amantadine is ‘off label’
- Used to reduce dyskinesia (37% reduction)
- Reduced OFF time by 45%
- Available in 2 doses
Osmolex ER (Amantadine)

- 1x daily amantadine
- Another 1x daily option, more for classic amantadine use without ‘off time’ reduction
- Cost
**ORTHOSTATIC HYPOTENSION**

**Northera**

- OH is common symptom of Parkinson’s Disease
- Can be worsened by dopamine supplementation
- Prodrug for Norepinephrine, crosses BBB
- Peripheral Nervous system – increased BP, improved Neurogenic Orthostatic Hypotension
- Central Nervous system – attention? Gait? Falls?

Nuplazid (Pimavanserin)

- First antipsychotic medication specifically designed for hallucinations and ‘psychosis’ associated with Parkinson’s Dementia and Lewy Body Dementia.
- Serotonin Agonist with no impact on dopamine receptors
- Novel drug status
- + SAPS-PD improvement with no change in UPDRS

HALLUCINATIONS AND PSYCHOSIS

Namzaric™ (Donepezil + Memantine)

- Once a day combination of the two agents
- Moderate disease to severe.
- Can be opened and sprinkled to administer.
PSEUDOBULBAR AFFECT

Nuedexta

- “Uncontrollable episodes of crying and/or laughing, or other emotional displays.”
- Disconnect between emotion and display, or inappropriate display

- PRISM study – 26%, though up to 40% in PD
- CNS-LS Screening reflects symptoms
- Reduction in episodes at 90 days was 72.3%.
But also non-LSVT Therapy aimed at balance/gait and strengthening
TECHNOLOGY

- DUOPA Intestinal Gel
- Focused Ultrasound
- Deep Brain Stimulation
Duopa

- Dopamine gel continuously administered via intra-intestinal pump
- Provides steady delivery of levodopa without the fluctuations of oral medication
- Off time decreased by 4h and on time increased by 4h


http://www.parkinson-italia.it/
FOCUSED ULTRASOUND (FUS)

- 1,000 ultrasound beams
- Non-invasive
- Creates focal lesion at target
- Approved unilateral ET, unilateral PD tremor
DEEP BRAIN STIMULATION (DBS)

1990s – DBS emerged as safer treatment with significantly longer duration of action compared to lesioning; no ‘burnout’.

- Surgically implanted device to deliver a controlled stimulation of electricity to a specific region of the brain.

- Implanted in 2 step procedure, then programmed as outpatient.

- Unlike previous surgeries for PD (pallidotomy or thalamotomy), DBS does not damage healthy brain tissue by destroying nerve cells.

- Removable, if necessary, with little to no tissue damage.*

The DBS system consists of three components:
- Intracranial Lead
- Extension connecting lead and generator
- Implantable pulse generator (neurostimulator)

- Unilateral or bilateral leads
- Proper patient selection is key
DBS INDICATIONS

- DBS is an FDA indicated surgical procedure for the treatment of movement disorders, such as:
  - Parkinson’s Disease
  - Essential Tremor
  - Dystonia

- FDA approved:
  - Essential tremor in 1997
  - Parkinson's disease in 2002
  - Dystonia in 2003

Covered by all insurance providers.
Parkinson’s Disease:

- 80-90% of patients note improvement
- 60% reduction in medications
- 60% reduction in dyskinesias
- 80% improvement in “off” periods
- 10% improvement in “on” periods
- 4.6 hours MORE on time without dyskinesia

Reduction in medications leads to decrease in the following:
- Cost
- Side effects (nausea, orthostasis, cognitive change, and downstream dyskinesia risk)
**Conclusions:** DBS was found to be superior to medical therapy in patients with PD and early motor complications.
REDUCTION IN MEDICATION COST AND POLYPHARMACY

- Medication costs over 24 months
  - Increased 72% in optimal drug therapy (ODT)
  - Decreased 16% in DBS+ODT
    - $7,150 cost savings over study period
    - Projected to 10 years – $64,590 savings

- Polypharmacy at 24 months
  - DBS+ ODT subjects were 80% less likely to require polypharmacy compared to ODT subjects
REDUCTION IN MEDICATION COST AND POLYPHARMACY

- Same group, followed out to 5 years
- Polypharmacy at 5 years
  - ODT increased from 43% to 93%
  - DBS+ODT from 36% to 43%

Conclusions: These results suggest that people with early stage PD treated with medications alone are 17 times more likely to require polypharmacy after five years compared to those treated with STN-DBS.

Subthalamic Nucleus Deep Brain Stimulation in Early Stage Parkinson’s Disease Reduces the Risk of Polypharmacy: Five-Year Analysis

Meeting: 21st International Congress
Abstract Number: 1341
Effects of deep brain stimulation on rest tremor progression in early stage Parkinson disease


**Results** UPDRS-III “off” rest tremor score change from baseline to 24 months was worse in patients receiving ODT vs DBS + ODT ($p = 0.002$). Rest tremor slopes from baseline to 24 months favored DBS + ODT both “off” and “on” therapy ($p < 0.001$, $p = 0.003$, respectively). More ODT patients developed new rest tremor in previously unaffected limbs than those receiving DBS + ODT ($p = 0.001$).

**Conclusions** These results suggest the possibility that DBS in early PD may slow rest tremor progression. Future investigation in a larger cohort is needed, and these findings will be tested in the Food and Drug Administration–approved, phase III, pivotal, multicenter clinical trial evaluating DBS in early PD.

**Classification of evidence** This study provides Class II evidence that for patients with early PD, DBS may slow the progression of rest tremor.
Essential Tremor:

- 80% improvement in tremor.
- 70% improvement in handwriting.
- Significant reduction in medications with possibility of stopping medication.

- Reduction in medications leads to decrease in the following:
  - Cost
  - Side effects (cognitive change, fatigue, lethargy, etc.)

BENEFIT FOR OUR PATIENTS

Pre DBS on high dose Primidone

Post DBS on no medication
A good candidate for DBS per our center:

1. Parkinson’s Disease at least 4 yrs (FDA indication)
2. Experiencing a response to medication
3. Experiencing the on-off fluctuation of medication
4. Able to participate in care
5. Good surgical candidate
6. No diagnosed dementia or severe psychiatric disorder
AN EXPANDING FIELD

- Directional stimulation
- Improved technology
- Smaller technology, thinner
- Longer battery life
DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM
DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM

4 = Full-ring contact

3 = Contact with equally spaced segments

2 = Contact with equally spaced segments

1 = Full-ring contact
DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM

Reference: Poster: VTA Modelling studies- Cheeran, Venkatesan, Kent- WSSFN 2017
DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM

Omnidirectional

Directional
COMPETITION ONLY BENEFITS THE PATIENT

3 years ago

Now

Medtronic

St. Jude Medical

Boston Scientific
A team approach is key to a successful outcome.

- Cognitive evaluation
  - Full Neuropsychiatric testing
- Psychiatric evaluation, if necessary
- Physical therapy, occupational therapy and speech therapy
- Neurosurgical evaluation
  - Work together for pre-surgical planning
    - GPI vs STN, Unilateral vs Bilateral
    - Intra-operative cooperation
- Movement Disorders Specialist
TO THE FUTURE

- Longer-acting levodopa formulations (10 hours or greater)
- New inhibitors
- Inhaled, sublingual, pump-based formulations
- Improved technology
- Targeted protein therapy
- Cure

All of this equals

HOPE
THANK YOU – Q&A WITH OUR TEAM

703-845-1500

www.inova.org/move