ADVANCEMENTS IN THE TREATMENT OF PARKINSON’S DISEASE

Neurorestoration and Beyond
WHAT IS PARKINSON’S?

1/100 OVER AGE OF 60

60,000 NEW

1M/US

5M/WORLD

NO CURE, MEDICATION ONLY HELPS WITH SYMPTOMS

There is NO TEST and no PROGRESSION MARKER

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.
WHY DOES PD CHANGE OVER TIME?

The disease itself AND medications used

[Diagram showing the change in levodopa response over time for Early PD, Moderate PD, and Advanced PD.]

Source: Schapira et al, 2009

[Graphs showing plasma dopa levels and disability over time with levodopa dosages.]
WHY DOES PD CHANGE OVER TIME?

Medications used – Classic 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
CARBIDOPA – LEVODOPA

Blood Levels of Levodopa

MILD  MODERATE  SEVERE

Early “Wearing OFF”  Delayed “ON”

Levodopa Administration

Dyskinesia
“ON” Time Therapeutic Window
“OFF” State

Fluctuations
**APPRAOCH TO THERAPY**

**Classic**
- Pulsatile and frequent
- Higher and higher doses

- Fluctuations
- Early side effects
- Treatment horizon

**Contemporary**
- Predictable and long acting
- Low doses, multiple targets
- “Rational polypharmacy”
- Employ technology earlier

- Smoother
- Reduced side effects
- Evergreen
EXPANDED TOOLBOX UP UNTIL 5 YEARS AGO

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

- Carbidopa/Levodopa formulation
  - AZILECT® (rasagiline tablets)

- MAOB inhibitor

- COMT inhibitor
  - Stalevo (levodopa, carbidopa and entacapone) tablets
  - COMTan® (entacapone) tablets
  - Parcopa® (carbidopa and levodopa orally disintegrating tablets)
NEW LEVODOPA FORMULATION

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


NEW MAO-B INHIBITOR, AUGMENTING THE SYSTEM

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
LONGER-ACTING AMANTADINE

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

![Graph showing Amantadine ER 274 mg QD (10 PM) and Amantadine IR 81 mg BID (8 AM & 4 PM)]
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

**Namzaric™ (Donepezil + Memantine)**

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

![Graph showing mean (SD) CNS-LS score changes](image-url)
PHYSICAL/OCCUPATIONAL/SPEECH THERAPY

But also non-LSVT Therapy aimed at balance/gait and strengthening
TECHNOLOGY

- DUOPA Intestinal Gel
- Focused Ultrasound
- Deep Brain Stimulation
**CONSTANT DELIVERY OF LEVODOPA**

**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\(^1\)

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http://www.parkinsonitaly.it/
FOCUSED ULTRASOUND

- 1,000 ultrasound beams
- Non-invasive
- Creates focal lesion at target
- Still in research

“So far, the jury is out. We are, after all, burning a hole in the brain.”
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.*

DEEP BRAIN STIMULATION (DBS)

- The DBS system consists of three components:
  - Intracranial Lead
  - Extension connecting lead and generator
  - Implanted 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

Research Report

Subthalamic Nucleus Deep Brain Stimulation May Reduce Medication Costs in Early Stage Parkinson’s Disease

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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
**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.)
WHO IS A CANDIDATE

- 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
OPTIONS = GOOD FOR PATIENTS

- **MEDTRONIC SYSTEM**
  - Has been around for 20 years.
  - Created the technology and built the industry.
  - Still a great system where people get better, and widely used.
  - MRI approved.
  - Non-Directional.
  - Voltage based.
  - Older technology

- **ABBOTT/ST. JUDE SYSTEM**
  - New player on the block.
  - Integrated the last 20 years of research.
    - Directional stimulation.
    - Current based.
  - Truly wireless and built on Apple platform – user designed.
  - Updateable.
  - Improved hardware, lower profile.
  - No MRI approval yet.
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
PARKINSON’S DISEASE
PARKINSON’S DISEASE
TO THE FUTURE

- Longer-acting levodopa formulations (10 hours or greater)
- New MAO-B and COMT inhibitors
- Inhaled or sublingual formulations
- Improved technology
- Targeted protein therapy
- Cure

All of this equals

HOPE
THANK YOU

INOVA
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