PARKINSON’S DISEASE IN 2020

Parkinson’s Fundamentals and Applying Updated Medical Options
INOVA PARKINSON’S & MOVEMENT DISORDERS CENTER
INova Movement Disorders Center

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WHAT IS PARKINSON’S?

1 in 100 over age of 60
60,000 new

1M in US
5M in 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.
WHAT CAUSE PARKINSON’S DISEASE?

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

NON-MOTOR SYMPTOMS
The symptoms of Parkinson's disease vary from person to person, but may include both motor and non-motor symptoms.

### Before Diagnosis
- Constipation
- REM sleep behavior disorder
- Reduced ability to smell
- Depression
- Fatigue
- Urinary symptoms

### After Diagnosis
- **Early**
  - Slowed movement
  - Rigidity
  - Tremor

- **Advanced/Late**
  - Difficulties speaking
  - Difficulties with posture
  - Freezing of gait
  - Falls
  - Urinary symptoms
  - Orthostatic hypotension
  - Dementia
When medication is not doing what it is expected to or can do

- Many different types of OFF, sudden or subtle
  - First AM off
  - End of dose
  - Sub-optimal on
  - Sudden off
  - Dose failure
  - Exercise-induced
  - Food-induced

- Motor and non-motor OFF

If we fix OFF, we fix Parkinson’s Disease.

Online survey of 3,000+

- 70% reported 2+ Off episodes a day.
- 65% reported 2 or more hours a day
- 50% – moderate/severe, affected daily activities
WHY DOES PD CHANGE OVER TIME?

Current debate - the disease itself AND medications used?

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
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GENERAL TREATMENT ALGORITHM

Varies based on:
- Experience
- Comfort
- Place of training
- Industry interaction
- Clinic structure and time
MEDICATION CATEGORIES FOR PD

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

Synapse (space between neurons)

**COMT inhibitors slow the breakdown of levodopa**

**Levodopa replaces dopamine**

**Dopamine agonists mimic dopamine**

**MAO-B inhibitors slow the breakdown of existing dopamine**

**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)
- Carbidopa/Levodopa formulation
- MAOB inhibitor
  - Azilect® (rasagiline tablets)
- COMT inhibitor
  - Stalevo® (carbidopa, levodopa and entacapone) tablets
  - COMTan® (entacapone) tablets
  - Parcopa® (carbidopa and levodopa orally disintegrating 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
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

**RESCUE OPTION #1 - APOKYN**

Mean Percentage of Off Episodes Reversed Over 4 Weeks in Outpatient Phase

- **95%** APOKYN-treated patients (n=17)
- **23%** Placebo-treated patients (n=8)

p<.001 vs. placebo
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 UPDRS Part III score change from 0-60 minutes postdose at Week 12.](image)

**Primary endpoint**
- Placebo (n=112)
- INBRIJA 84 mg (n=114)

**Improvement**
- Least squares mean (± SE) change from prescore

- Time postdose (min)
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
Nourianz

- INDIRECT pathway – activation reduces motor activity
  - Direct pathway increases activity (dopamine, etc.)
  - Indirect pathway inhibits motor activity (adenosine, GABA)
- Adenosine A2a receptor antagonist
  - Double negative, blocks the block
- Improves off time, releasing the ‘brake’ on the system.

**BLOCK THE INDIRECT PATHWAY**
Opicapone

- JUST APPROVED BY FDA
- “Add on” therapy to treat “off” episodes.
- Peripherally acting COMT-inhibitor
- 1x daily (instead of 4-5 daily)
  - Half life of 94 hours.
- Blocks breakdown of levodopa in the periphery, making more available to the brain.
- In use in Europe since 2016.
**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

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
NEW TOOLBOX...AND GROWING

- Dopamine Agonist
- Carbidopa/Levodopa formulation
- MAOB inhibitor
- COMT inhibitor
- A2a agonists
- Amantadine derivatives
- Rescue Therapies
- Symptom specific therapies

MOVEMENT DISORDERS
SPECIALTY CENTER
GENERAL TREATMENT ALGORITHM

Now more complex. Two MUSTS to navigate:

1) NEED MOVEMENT DISORDERS TEAM

2) TAKE CLINICAL DECISION FROM BASICS OF DOPAMINE DEFICIENCY AND TARGET SPECIFIC SYMPTOMS/LIMITATIONS
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
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THANK YOU – Q&A WITH OUR TEAM

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Find us on Facebook!
PARKINSON’S DISEASE IN 2020

Advanced Therapies: DBS, Duopa and more
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BEFORE DIAGNOSIS

Early
- Constipation
- REM sleep behavior disorder
- Reduced ability to smell
- Depression
- Pain
- Fatigue

After Diagnosis

Advanced/Late
- Difficulties speaking
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Motor
- Slowed movement
- Rigidity
- Tremor

Non-motor
- Urinary symptoms
- Orthostatic hypotension
- Dementia

Time (years)

Degree of Disability
When medication is not doing what it is expected to or can do

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CARBIDOPA – LEVODOPA

Blood Levels of Levodopa

MILD

MODERATE

SEVERE

Levodopa Administration

Early “Wearing OFF”

Delayed “ON”

Dyskinesia

“ON” Time
Therapeutic Window

“OFF” State

Fluctuations
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TREATMENT ALGORITHM FOR THE MANAGEMENT OF PARKINSON’S DISEASE

Parkinson’s disease

Nonpharmacologic intervention

Pharmacologic intervention

Neuroprotection — ? Rasagiline

Functional disability

Yes

No

Dopamine agonists

MAO-B Inhibitor

Combination therapy

Levodopa/dopamine agonist/COMT Inhibitor/MAO-B Inhibitor

Surgery/CDS

Varies based on:
- Experience
- Comfort
- Place of training
- Industry interaction
- Clinic structure
- and time

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
- Implanted pulse generator (neurostimulator)

- Unilateral or bilateral leads

- Proper patient selection is key
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.
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
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
DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM
DIRECTIONALITY, THE PRESENT AND FUTURE OF STIM

Reference: Poster: VTA Modelling studies- Cheeran, Venkatesan, Kent- WSSFN 2017
COMPETITION ONLY BENEFITS THE PATIENT

3 years ago

Medtronic

NOW

Medtronic

Abbott

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
Longer-acting levodopa formulations (10 hours or greater)
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