Disclosures

- I have no relevant financial relationships to disclose with commercial interests to disclose.
Essay on the Shaking Palsy, 1817

Dr. James Parkinson
1755 - 1824

An Essay on the Shaking Palsy.

By James Parkinson, Member of the Royal College of Surgeons.

London: Printed by Whittingham and Rowland, Gracechurch Street; For Sherwood, Neely, and Jones, Paternoster Row. 1817.
Parkinson’s Disease

- **Neurodegenerative** disease caused by loss of **dopamine** producing cells in the basal ganglia
- **>1 million** patients in the US
- Higher incidence in whites than African Americans or Hispanics

- Cultural disparity – Biological differences vs barriers to healthcare vs cultural beliefs about health and aging.
Idiopathic Parkinson’s Disease (PD)

- Cardinal Features (require 2 of 3 for diagnosis)
  - **Rest Tremor** – Usually begins in one hand and is described as “pill-rolling”
  - **Bradykinesia** - Slowness in movement
  - **Rigidity** – Stiffness in arms and legs
  - **Postural Instability** – Stooped posture when standing and poor equilibrium
  - **Gait Disturbance** - Shuffling feet with the initiation of gait and turns
Dopaminergic Neuron Loss in PD

% Remaining

Dopaminergic Neurons

Onset

Pre-symptomatic phase

Sleep

Olfactory* (may predate clinical PD by at least 4 years)

Mood

Autonomic system

Early non-motor symptoms

Non-motor

Specific symptoms

Motor

Time (years)

*Olfactory dysfunction may predate clinical PD by at least 4 years.
The goal is to improve the symptoms of tremor, bradykinesia, and rigidity by modulation and replacement of dopamine levels through oral medications.

- Carbidopa/levodopa
- COMT-inhibitors
- MAO-B inhibitors
- Anticholinergic agents
- Antiviral agents
Drug Therapy

1) **Levodopa** (Sinemet, Rytary) – Dopamine replacement

2) **MAO-B Inhibitors** (Azilect, Selegiline, Zelpar) - Inhibit the breakdown of dopamine

3) **Dopamine Agonists** (Mirapex, Requip, or Neupro) – Mimic dopamine by stimulating the dopamine receptor sites directly

4) **Entacapone or Tolcapone** (Comtan or Tasmar) - Increase the duration of effect of L-dopa

5) **Amantadine**: Reduce L-dopa induced dyskinesias
Sinemet (carbidopa/levodopa)

- **L-DOPA** is co-administered together with **Carbidopa**, so it is not converted to dopamine before it crosses the blood brain barrier.

- **Carbidopa** prevents undesirable side effects of dopamine release into the PNS, including nausea.
Sinemet (carbidopa/levodopa)

- **Levodopa** improves motor symptoms and is the most effective PD therapy available (gold standard).
- All patients eventually require levodopa and it continues to provide benefits during the course of the disease.
- There is no evidence that levodopa accelerates the disease and it improves overall mortality and morbidity.
Carbidopa/Levodopa

1. Advantages

- Most effective Parkinson’s medication (Gold Standard of therapy)
- Well tolerated by many people
- Rapid absorption
Carbidopa/Levodopa

2. Disadvantages

- Does not treat all Parkinson’s symptoms
- Half life of Sinemet is short (90 min.) and duration of action is 3-4 hrs.
- Does not stop progression
**Limitations:**

- after 5-10 years: motor fluctuations and involuntary movements called dyskinesias occur

- Alterations of “on” periods (with or without dyskinesias) and “off” periods during the day.
Carbidopa/Levodopa

- **ON period** – Medications are effective and controlling symptoms
- **OFF period** – Reemergence of symptoms occurs when the medication wears off
- **Levodopa dyskinesia** – Occurs at peak dose
Carbidopa/Levodopa

- Motor Fluctuations

![Graph showing motor fluctuations with L-dopa injections and 'ON' and 'OFF' states over time](image-url)
Carbidopa/Levodopa

3. Side Effects
- Motor complications (dyskinesias, “on/off”)
- Neuropsychiatric problems (confusion, psychosis, delusions, etc.)

4. Strategies to improve motor fluctuations:
- Take levodopa 60 minutes before protein or 2 hours after protein intake
- Protein intake at the end of the day
MAO-B Inhibitor

- **Selegiline** – Mild symptomatic benefit with amphetamine metabolite
- **Zelpar** – Oral disintegrating form of Selgiline with fewer side effects
- **Rasagiline (Azilect)** – Newest MAO-B inhibitor with increased symptomatic benefit and anti-apoptotic effect
MAO-B Inhibitor

1. Advantages

- Mild symptomatic benefit with mono-therapy in early PD and possibly delays progression (Adagio trial)

- Add on therapy to L-dopa or DA to improve motor fluctuations

- May improve freezing of gait

- Typically tolerated very well
MAO-B Inhibitor

2. Disadvantages

- May worsen levodopa induced dyskinesias with add on therapy

- Interactions with medications:
  
  Meperidine, Tramadol, Methadone, Propoxyphene, Dextromethorphan, St. John Wort, Cyclobenzaprine
3. Side effects - Dyskinesia, confusion, psychosis

4. Strategies – Take in AM to maximize effect
Dopamine Agonists

- Early DAs were ergot derived and removed from the market due to valvular heart disease
  - Pergolide and Bromocriptine
- Pramiprexole, Ropironole, Apokyn, Rotigotine
Dopamine Agonists

1. Advantages

- Mimics the effect of dopamine and is effective monotherapy and add on therapy
- Longer lasting than levodopa (Mirapex ER, Requip XL, Neupro patch)
- Lower risk of motor fluctuation and dyskinesia
Dopamine Agonists

2. Disadvantages

- Not as effective of a therapy as levodopa
- High risk of side effects in patients > 65
- Severe behavioral side effects (ICD)
Dopamine Agonists

3. Side effects
   - Impulse control disorder (ICD): gambling, hypersexuality, compulsive buying, etc.
   - Sleep attacks, psychosis, leg edema, N/V

4. Strategies – Report any behavior change ASAP
COMT Inhibitors

- Catechol-O-methyltransferase (COMT)
  - Comtan or Stalevo and Tasmar
- Blocks degradation of levodopa

1. Advantages:
   - Prolongs LD half-life and improves wearing off and motor fluctuations
   - Delays fall in concentration of LD

2. Disadvantages – May worsen dyskinesia
3. Side effects
- orange colored urine, diarrhea, dyskinesias, psychosis, confusion, dizziness, etc.

4. Strategies
Take every dose with levodopa, since it is ineffective alone
Amantadine

- Glutamate/NMDA receptor antagonist
- Enhances dopamine release

1. Advantages
   - Only medication available to reduce dyskinesia which improves quality ON time

2. Disadvantages
   - Older patients have increased risk of confusion and psychosis
Amantadine

4. Side effects

- leg edema, skin changes (livedo reticularis)
- insomnia, vivid dreaming, psychosis

5. Strategies

Avoid taking amantadine in the late afternoon since it can interfere with sleep
Medical Therapy Summary

- MAO-B Inhibitors or Dopamine Agonists are typically used in early PD to delay L-dopa complications, unless patients are older (>70).
- L-dopa should then be added once DA is no longer effectively controlling symptoms or if patient is having side effects.
- L-dopa dose should be started at low dose and increased slowly to adequate dose to control symptoms and delay complications.
New Medication Options

- **Rytary** – CD/LD extended release cap
- **Duopa** – CD/LD enteric suspension
- **Nuplazid** – antipsychotic for PD psychosis and delusion
- **Northera** – orthostatic hypotension
The new Levodopa...45 years later

- January 8th, 2015 FDA approved RYTARY, an extended-release oral capsule formulation of carbidopa-levodopa, for the treatment of PD.
- January 12th, 2015 FDA has approved DUOPA™ (carbidopa and levodopa) enteral suspension for treatment of motor fluctuation for people with advanced PD
Levodopa Therapy - Rytary

- **Extended-release carbidopa/levodopa:**

  **Rytary** – capsule which contains IR and ER beads with 3-5 times per day dosing. Provides initial peak at 1 hr and maintain level for 4-5 hrs

  - Reduce off time by 2.2 hrs/day more than Levodopa IR and 1.5 hrs/day more than Stalevo
Levodopa Therapy - Rytary

Initial peak
- Achieved initial peak plasma concentration at about 1 hour.¹

with...

Extended release
- Maintained plasma concentrations for about 4 to 5 hours before declining.¹
Rytary Strategies

- Take 1 hour before or 2 hours after protein

- Parkinson’s symptoms may worsen since the dose may be under-dosed by the conversion table formulated by the company

- Patient’s Rytary dose is typically 1.5 to 2 times the previous Sinemet dose (bioavailability is 70%) and patient on Stalevo will need an even higher dose

- May take 4-6 weeks to obtain correct dose
Levodopa Therapy – Duopa Enteric Suspension

Gel formulation of carbidopa/levodopa delivered directly into the small intestine via a tube. Duopa requires a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) for drug delivery.

- Indicated for advanced Parkinson’s and compared to Sinemet IR with 2 hours less OFF time and increase of 2 hours ON time.
Duopa Administration

- Duopa is continuously administered over 16 hours with the CADD-Legacy® 1400 pump.

**Duopa treatment during the day**

**Oral Parkinson's disease (PD) medication at night**

- Oral PD medication at night
- Duopa for up to 16 hours per day
- Extra Doses are self-administered as needed
- Disconnect from infusion pump

Duopa [package insert]. North Chicago, IL: AbbVie Inc.
Duopa Administration

- Daily doses include morning dose, continuous dose, and extra doses as needed
- Pump is disconnected at the end of the daily 16-hour infusion
- Patients should be prescribed a supply of oral immediate-release (IR) carbidopa-levodopa tablets in case they are unable to administer the Duopa infusion during the day
Non-motor Symptoms of PD

- Cognitive impairment
- Depression
- Fatigue
- Anxiety
- Orthostatic hypotension
- Psychosis
Orthostatic Hypotension

- Orthostatic hypotension is a drop in blood pressure upon standing causing dizziness, fainting, falling, etc.
- Norepinephrine maintains BP with change in posture
- Droxidopa (3-4 L-threo-DOPS) is NE precursor
Orthostatic Hypotension

- FDA approved Northera (Droxidopa) in 2014 for neurogenic orthostatic hypotension
  - Study reveals reduction in dizziness, and increased standing BP after week 1
  - Rates of falls reduced (0.38 vs 1.73/week)
  - Most common side effects: headache, HTN, nausea
**Psychosis**

- PD psychosis affects a large number of patients and is the leading cause of nursing home placement.
- Seroquel and Clozaril are used to treat PDP but have limitations.
- All other antipsychotics (typical or atypical) should be avoided since they will worsen motor symptoms.
Psychosis

• FDA approved Pimvanserin (Nuplazid) 5 HT2A antagonist on April 9th, 2016.

• Decreased psychosis compared to the placebo, including improvements in nighttime sleep, daytime wakefulness, and caregiver burden

• Most common side effects were UTI and leg edema; there was no worsening in motor symptoms

• May prolong the QT interval and should be avoided in patients with known QT prolongation or in combination with other drugs that prolong QT interval
Tips for Success for PD patients

- Take medications on a regular schedule and try to take Sinemet at least 1 hour before protein intake.

- Record bothersome symptoms and observe if they occur at a certain time of the day in relation to the medication schedule.

- Exercise on a daily basis since the benefits are similar to medications and likely slows progression of the disease.