ABCs of Early Diagnosis and Management of Parkinson’s

Mary (Molly) Scott RN, MSN, FNP-BC
Parkinson’s and Movement Disorder Program
Associate Clinical Professor
University of Toledo College of Medicine
UTCOM- Promedica Neuroscience Center
Disclosures

• Speakers Bureau:
  – Acorda, Amneal, Adamas

• Parkinson’s Foundation
  – Edmond J. Safra Visiting Nurse Faculty Program
Objectives

- Identify the motor and non-motor symptomology of Parkinson’s disease
- Define clinical features (motor) and criteria for diagnosis of PD
- Identify different PD therapies
- Recognize adverse effects of PD meds
- Compare and contrast management styles of Parkinson’s disease at various stages of the disease
4 Cardinal Symptoms of PD
Must have Bradykinesia and 1 other symptom to meet criteria for clinical diagnosis of PD

• Bradykinesia-slowness of movement
  – must be present and usually is unilateral in onset
• Tremor primarily at rest
  – and occurs in about 50-60%
• Muscle Rigidity
  – To passive manipulation of extremity
• Postural Instability
  – Often seen later in disease progression- red flag if early symptom. Retropulsion
Common Early features

- Stooped posture
- Small handwriting
- Decreased arm swing
- Changes in facial expression
- Shuffling walk

Pre-Motor symptoms can occur years before motor symptoms

- Hyposmia – loss of sense of smell
- REM Behavior sleep disorder – taking out and acting out in sleep
- Restless legs
- Neurogenic Orthostatic hypotension
- Constipation
- Depression
Non-Motor Symptoms

- **Sensory** - shoulder pain, dystonia, paresthesia, restless leg syndrome
- **Autonomic** - Neurogenic orthostatic hypotension (NOH), sweating, sialorrhea, rhinorrhea, bladder urgency, frequency, incontinence and erectile dysfunction.
- **Sleep disorders** - fragmentation, REM sleep disorder, excessive daytime sleepiness, drug induced sleep attacks
- **Fatigue**
- **GI** - constipation, gastroparesis, dysphagia
- **Psychiatric** - apathy, depression, anxiety, impulse control, hallucinations, delusions
- **Cognitive** - Mild cognitive impairment and PD dementia
Basal Ganglia

https://commons.wikimedia.org/wiki/File:Brain_structure.png
Pathophysiology

Nigrostriatal degeneration
• Loss of pigmented dopaminergic neurons in the substantia nigra pars compacta
• 60-80% reduction in striatal dopamine uptake before PD motor onset
• Involvement of other neurotransmitter systems: cholinergic, noradrenergic and serotonergic
• Loss of dopaminergic neurons increase inhibitory output of the basal ganglia and hypokinetic movement

Lewy bodies (alpha-synuclein) in the Substantia nigra Pars compacta
Clinical Course of Parkinson’s Disease

- Pre-symptomatic phase of disease for several years with elevated loss of DA neurons

- Clinical symptoms observed

- Disease severity

- DA Neurons

- Drug therapy needs increase and AEs start

Dx Time
Imaging

- Not required for dx but ruling out other possible causes is sometimes needed
- MRI brain- no contrast
- DAT Spect Scan- only helps to differentiate tremors (essential versus PD) but does not rule out other PD like conditions
- No serum or blood test or biomarkers at this point in time.
DAT Spect Scan
Measures dopamine transporter (DaT) in Basal Ganglia only FDA approved to distinguish potential Parkinson’s disease from essential tremor.

Cost of a DAT scan ranges from $2,500-5,000.
Dopamine Synthesis and Metabolism

Presynaptic Terminal

Tyrosine → Tyrosine hydroxylase → Dopa → Dopa decarboxylase → DA

DA receptor

Postsynaptic Terminal

Expressing either D1 or D2 receptors

DA = Dopamine

HVA

MAO → COMT

3MT

DOPAC

G-protein signalled response

Adapted from Adler et al. Parkinson's Disease and Movement Disorders. Totowa, NJ: Humana Press; 2000:64.
Factors That Influence Choice of Treatment

- Patient age
- Cognitive and psychiatric status
- Symptom severity - ability to perform ADLs
- Comorbidities
- Employment status/domestic responsibilities
- Social life and lifestyle
- Development of motor complications with long-term L-dopa treatment
Levodopa Therapy in PD

- Gold standard of PD therapy since 1971
  - (Watch the movie Awakenings with Robin Williams)
- Levodopa is always given with carbidopa
  - Carbidopa helps the levodopa get to the brain by inhibiting breakdown by enzyme dopa-decarboxylase
  - Decreases nausea associated with levodopa
- Most efficacious symptomatic drug for PD
- Compared to untreated patients, levodopa increases survival and QOL
- Long-term use may be associated with motor complications—especially dyskinesia
Levodopa Formulations

- Carbidopa/Levodopa (immediate release) Sinemet 25/100, 10/100, 25/250
  - C-Max 15-45 minutes
- Parcopa (C/L oral disintegrating IR) 25/100
- Carbidopa/Levodopa ER, SA
  Sinemet CR 25/100, 50/200
  - C Max 2-3 hours
  - slightly longer acting than IR. Absorption is more variable. Bioavailability about 75% of the C/L IR dose
- Carbidopa (Lodosyn) 25 mg - is available to help reduce nausea if the C/L is not tolerated.
Levodopa Formulations

• Rytary
  – new formula longer acting Carbidopa/levodopa
  – Capsules with small beads of variable absorbing C/L, dosing q6-8 hours
  – Capsule can be opened and put into applesauce, should not chew the beads, also can be given if suspended in viscus solution through feeding tube
  – Dose of Rytary in milligrams is not equivalent to carbidopa/levodopa, about ½ as potent
  – Rytary doses are: 23.75/95, 36.25/145, 48.75/195, 61.25/245 mg
Levodopa Formulations

Combination drug
(Stalevo) carbidopa/levodopa IR/entacapone.

- Stalevo 50 = 12.5/50/200
- Stalevo 75 = 18.75/75/200
- Stalevo 100 = 25/100/200
- Stalevo 125 = 31.25/125/200
- Stalevo 150 = 37.5/150/200
- Stalevo 200 = 50/200/200
Choosing Levodopa Therapy

- **IR:** rapid absorption and shorter distribution curve (nausea producing especially with initial therapy)
- **ER:** absorption more prolonged and less consistent (less nausea producing)
- **Rytary:** both long and short acting in one capsule not available as a generic

Patients can be treated with more than one of these therapies together
Levodopa Therapy

• Initial starting dose: start slow

• Carbidopa/Levodopa IR or ER 25/100
  – ½ or 1 tab po tid with meals.

• After 2-4 weeks switch to 60 minutes before meals. Usually given 3 times daily, every 4-5 hours depending on formulation

• **Protein will inhibit absorption- give 30 to 60 minutes prior to meals.**

• If nausea can take with toast and honey, carbs.
Side Effects with Levodopa

- Nausea
  - Especially with initiation of therapy
- Abnormal dreaming
- Dizziness
- Dry mouth
- Constipation
- Headache
- Sleepiness
- Insomnia, difficulty falling asleep or staying asleep.
- Dyskinesia
- Wearing off
Levodopa Therapy

- With time and disease progression the **timing of doses becomes critical**
  - dosing every 3-4 hours 4 or 5 times a day and sometimes more frequently
  - Even 15 minute delay in dose can cause “wearing off”
- Most often dosing occurs during day – dopamine not needed at night.
  - Doses at night or before bed is sometimes too stimulating and can inhibit sleep.
  - Exceptions for those that have significant off times overnight
- Timing prior to consumption of meals/protein becomes more critical.
- ECF and hospitalized patients suggested doses at 6am-10 am-2pm
  - to avoid delayed dose from shift change
Definitions

• ‘On’ time
  – A period of relatively good overall function and mobility

• ‘Off’ time
  – A period of relatively poor overall function
    • Worsening tremor, rigidity, bradykinesia or balance

• Dyskinesia
  – Involuntary- wiggly or swaying movements
    • Most often when doses peak but can be with wearing off

• Freezing
  – Inability to initiate or sudden halt in movement
Long-term use of levodopa may be associated with motor complications and fluctuations in symptoms.

Adapted from Waters Figure 3, reprinted from Stern, 1993.
Dopamine Agonists

- Stimulate dopamine receptors (D₂) at post synaptic terminals - Mimics dopamine
- Can be used as initial monotherapy or add on therapy
  - Ropinirole (Requip) short and extended release
  - Pramipexole (Mirapex), short and extended release
  - Rotigotine (Neupro-patch) transdermal
  - Apomorphine (Apokyn) injectable Sub Q Short acting for rescue for wearing off
  - Apomorphine HCL (Kynmobi) sublingual film
Adverse Effects with Dopamine Agonist

- Nausea
- Excessive Daytime Sleepiness and or sleep attachs
- Compulsive/Impulsive Behaviors
  - Gambling, hypersexualality, shopping, computer games, hobbies, etc.
- Hallucinations/delusions
- Memory impairment/loss
- Edema in lower extremities
- Higher AE rates than LD, use with caution in >65-70 yrs
COMT Inhibitors

- Catechol-O-methyltransferase (COMT) inhibitors
- Blocks degradation of levodopa in gut and periphery
- **Only works when given with C/L**
- More Levodopa reaches the CNS
  - Prolongs LD half-life
  - Delays fall in plasma concentration of LD

Entacapone (Comtan)

Opicapone (Ongentys) recently FDA approved, once daily dosing at bedtime

Tolcapone (Tasmar)- liver toxicity, monitor LFT
Adverse effects with COMT inhibitors

• Dyskinesia may be seen with all COMT-Inhibitors
  – Entacapone:
    • Orange discoloration of urine
    • Diarrhea- will not improve, usually stop med if this occurs.
    • Abdominal Pain, nausea
    • Fatigue
  – Opicapone:
    • Constipation
    • Elevated creatinine kinase
    • Hypotension
    • Weight loss
  – Tolcapone: rarely used due to liver toxicity
MAO-B Inhibitors

• Monoamine Oxidase
  Enzyme that degrades catecholamines—
  dopamine, norepinephrine, serotonin

• **MAO-A** ⇒ liver and gastrointestinal tract

• **MAO-B** ⇒ primarily in the brain
  — Rasagline 0.5 mg or 1 mg once daily
    (May take 2-3 months to get to full benefits, can be used as monotherapy or add on therapy)
  — Selegiline 5 mg 2 times daily in am adjunctive to L-dopa
    (not given in evening as it can cause insomnia)
  — Safinamide (Xadago) 50 mg daily to start then increase to 100 mg daily adjunctive to L-dopa
Adverse Effects with MAO-B inhibitors

- Lightheadedness/dizziness (Postural hypotension)
- Nausea/abdominal pain
- Vomiting
- Hallucinations
- Dry mouth
- Vivid dreams
- Dyskinesia
- Headache
Other PD Therapies

• Amantadine (Symmetrel) antiviral agent
  Effective for tremor and also for dyskinesia

• **Gocovri** new FDA approved long acting form of amantadine for treatment of dyskinesia. Given once daily at bedtime.

• **Osmolex** new FDA approved long and short acting form of amantadine. Given once daily in AM

Adverse effects: Confusion, hallucinations, insomnia-
(avoid use after 3 pm except Gocovri), livedo reticularis (rash or purplish mottling of skin), blurred vision, dry mouth.
Anticholinergic Agents

- Fallen out of favor in light of newer therapies
- Block nerve impulses to control muscle contractions in arms, legs, body
- Restrict action of acetylcholine
- Used for more than 100 years
- Side effects are common
- Useful in patients less than 65-70 years
- Most helpful for tremor relief
Anticholinergics and common side effects

Trihexyphenidyl (Artane)
Benztropine mesylate (Cogentin)
Ethopropazine (Parsitan)- from Canada or compounding pharmacy

- Gastrointestinal: Nausea, Xerostomia-dry mouth
- Neurologic: Dizziness
- Ophthalmic: Blurred vision
- Psychiatric: anxiety/nervousness, memory loss, hallucinations
Questions?