Pathology and Incidence

- First described in 1817 by James Parkinson
- Loss of dopamine neurons
  - 50% cell loss triggers onset of symptoms
- Over 1.5 million in North America Have PD diagnosis (0.3% of population). Project >50,000 new cases each year
- Average age of onset: 60 years
- Onset before age 40
  - Dystonia seen more often (may have painful curling of fingers or toes)
- 60:40 male preponderance
How Can We Dx PD Sooner
Why does it matter

• PD does not originate in the SN. Rather, pathologic change in the olfactory region (inhalation), areas around vagus nerve which innervate the gut (hence, effect on constipation), and brainstem (sleep disorders and autonomic system). It progresses to basal ganglia and SN and produces the motor symptoms that characterize PD. Pathology may progress to frontal regions thus producing the cognitive decline and dementia that can occur.
• Alpha synuclein found in colonic mucosa up to 5 years prior to diagnosis. Therefore, it is thought that the entries for this is from inhalation and/or swallowing, causing disease to actually begin in the peripheral system rather than CNS. May also be able to measure in CSF and serum so may be marker at some point
• Genetics:
  • Many genes have been discovered that are potentially associated with increased potential risk of PD
  • not everyone with genes get PD. Very low percentage of patients.
  • www.pdgene.org for information. Genetic testing used for clinical trials and future target therapy
Atypical Features of Parkinsonism

• Rapid progression
• Early onset dementia or hallucinations
• Early onset of balance difficulties or falls
• Early signs of autonomic dysfunction
• Abnormal eye movements
• Lack of response to Levodopa
• Important to recognize this, as management will change
Consider other Dx

- **Drug-Induced**
  - Chlorpromazine, Haloperidol, Olanzapine, Risperidone, Prochlorperazine Metoclopramide (reglan for n/v), Promethazine (phenergan for n/v), tegretol

- **PSP** (progressive supranuclear palsy): rapid progression, early falls (often good stride length), facial dystonia, slow saccades. One variant may only affect LE, with freezing.

- **MSA** (multi system atrophy): rapid progression, early falls, ataxia, dysarthria, impaired smooth pursuits, inspiratory stridor, myoclonus, facial dystonia (to stimulus), facial/feet dyskinesias, pisa syndrome (trunk pulled to one side); normal olfaction noted in MSA

- **DLB** (Dementia with Lewy Bodies): early visual hallucinations, rapidly progressive, cognitive fluctuations

- **NPH** (Normal Pressure Hydrocephalus); gait apraxia, cognitive decline, urinary incontinence

- **Vascular** Parkinsonism; lack of response to L-dopa, non or slowly progressive, MRI findings of stroke.
• Pharmacologic (medication) and non-pharmacologic (holistic) approaches are used for motor and non-motor symptoms to reduce the severity of symptoms and maintain optimal function and quality of life
• NOT EVERYTHING IS PARKINSON DISEASE
Treatment of PD

• Pharmacological
  • Dopaminergic:
    • **Levodopa/Carbidopa** (Sinemet, Rytary, Inbrija, Duodopa).
    • **Duodopa**: Enteral solution of carbidopa/levodopa inserted via Peg J tube into Jejunum where l-dopa absorbed. No improvement of dyskinesias (but not worse either).
  
• NON DOPAMINERGIC:
  • Dopamine Agonists (Pramipaxole, Ropinirole, Apomorphine)
  • MAO-B Inhibitors (Selegiline, Rasagiline, Xadago/Safinamide)
  • COMT (catechol-o-methyltransferase) Inhibitors (Entacapone/Comtan)
  • Nourianz: istradefylline: antagonizes adenosine receptor
  • **Amantadine** (not approved) and Gocovri (amantadine XL)
  • Anticholinergics: trihexiphenidyl (artane) and Benztropine (cogentin) for tremor that does not respond to dopamin replacement. Benadryl is antihistamine with mavanserin): only medication approved for delusions and hallucinations
  • Neudexta: dextromethorphan/quinidine: treats pseudobulbar affect
Treatment Side Effects

- L-dopa/carbidopa (sinemet, parcopa, Rytary, duopa intestinal gel)
  - Nausea (try zofran – not compazine or phenergan), wearing-off, dyskinesias, dystonia. Protein can interfere
  - Dyskinesias develop in 50% of people after 5 years and 70% after 15 years
- Dopamine Agonists (DA); pramipaxole, ropinirole, rotigatine (patch), apomorphine (injectable)
  - Impulse control disorder and not as effective as L-dopa, somnolence, visual hallucinations, peripheral edema, OH
- MAO-B inhibitors (rasagiline/selegiline/xadago)
  - n/v, OH. Fewer side effects than DA but not quite as effective
  - Selegiline can cause insomnia
- COMT inhibitor (comtan)
  - Urine discolored orange, diarrhea
- Adenosine antagonist (Nourianz)
  - SE: dyskinesias, dizzy, constipation, nausea, hallucinations, insomnia. Rare – psychosis (delusions, agitation, OCD)
- Dextromethorphan/quinidine: Neudexta
  - Diarrhea, dizziness, asthenia, cough, vomiting, peripheral edema, UTI, muscle spasms, QT prolongation, thrombocytopenia, respiratory failure
- Anticholinergics
  - Dry mouth, fatigue, confusion, hallucinations, constipation, urinary retention.
- Amantadine /Gocovri
  - Hallucinations, Constipation, Livedo Reticularis (caucasions/shins) and possible mild facial myoclonus
Treatment (a lot of options and variations)

- Early PD can start with Sinemet, Dopamine agonist, or MAO-B inhibitor
- If tremor predominant with mild rigidity and <65yo may start with DA or MAO-B. Maybe try Artane or Cogentin
- If >65yo depending on level of symptoms start with DA or L-dopa. If symptoms interfere with ADLs or have postural instability, start with L-dopa
Wearing Off

• Initially (first 0-5 years), L-Dopa has long duration >5 hours
• As disease progresses (6-10 years), duration declines to 3-5 hours and may develop dyskinesias
• In advanced disease (>10 years), short response with narrow window of effectiveness (2-3 hours)
• Document when symptoms increase or additional complications (etc. prior to next dose, dyskinesias at peak?).
• Confirm taking doses correctly
• For sudden wearing off you can
  • Crush IR levodopa and put in juice or applesauce
  • Apokyn injection
  • Inbrija (inhaled levodopa)
What if Medications Fail

• For fluctuations, try smaller doses more frequently; Try Rytary, add a DA, COMT or MAO-I, adenosine antagonist (nourianz)
• Medications no longer adequately controlling motor symptoms or develop disabling dyskinesias
• Or unable to tolerate medications due to side effects
  • Consider DBS, duodopa (infusion)
Treatment of non-motor symptoms

• REM sleep behavior disorder
  • Should try Melatonin first. Clonazepam small dose at hs.
  • Treat OSA if present
• Constipation
  • Miralax, high fiber diet, plenty of fluid, exercise
  • Start with fiber, then add Miralax, and then add docusate sodium (colace)
• Anxiety
  • 25-50% suffer from this. Can be off-symptom. Described also as restlessness and internal tremor. Can try SSRI such as venlafaxine, Benzodiazepines (sparingly)
• Apathy
  • More of problem with family, because person with PD “doesn’t care”. DA may help since it effects D2 and D3 receptors. Also can try Rivastigmine (exelon) even if no dementia
Treatment of non-motor symptoms

• Fatigue
  • 50% suffer from this. Difficult to treat. May increase from depression/anxiety. Take fewer naps during day to help sleep better at night. Practice good sleep hygiene for better night time sleep. May try provigil/nuvigil/modafinil.

• Drooling
  • Suck on hard candy, chewing gum
  • 1% atropine ophthalmic drops under tongue
  • Intra-parotid botox
  • If excessive phlegm, can try mucinex

• Urinary Frequency
  • Most medications used have anti-cholinergic properties so Ses
    • SE: dry mouth dizziness, constipation, fatigue, nausea, A, blurred vision, confusion, HTN, hallucinations
  • Mirabetriq new without as many anti-cholinergic side effects
Treatment of non-motor symptoms

- **Orthostatic Hypotension**
  - Keep hydrated, wear pressure hose and/or abdominal binder, do not avoid salt, sleep with head/chest elevated ~45 degrees. Florinef (fludrocortisone) volume expander long acting so not if supine hypertension. “Droxidopa (Northera) approved for PD, midodrine are short acting

- **Supine Hypertension** - can cause end organ damage and stroke risk
  - Sleep with head/chest elevated. Avoid decongestants, reduce fluid at bedtime, NO elastic socks when supine, no ‘pressors’ such as droxidopa or midodrine with 6 hours of bedtime and avoid long acting expanders such as fludrocortisone.

- **Depression**
  - Hard to treat. Get help from Psychiatrist if no response with one trial
  - Consider counseling. SSRI: Paroxetine nnt=14; SNRI: venlafaxine (effexor), (cymbalta/duloxetine). Bupropion (inhibits uptake of norepineprine and dopamine);
Treatment of non-motor symptoms

- Cognitive problems (more executive function and visual-spatial problem)
  - MOCA (Montreal Cognitive Assessment exam) annually or if there is concern
  - Rivastigmine/Exelon (FDA approved)
- Psychosis: Nuplazid (only med approved). Quetiapine (Seroquel)
  - First adjust levodopa, withdraw anticholinergics, adjust DA
  - All antipsychotics have increased risk of morbidity and ER visits (OH, Dizzy, sedation and CVA). Quetiapine less than others but still risk
Non pharmacologic

- Physical Therapy, Occupational Therapy and Speech Therapy
- EXERCISE!!!
- Music Therapy
- Massage
- Cognitive Behavior Therapy/Biofeedback
- Nutritious diet
- Support Structures (Support Group, Church, Family, Friends)
Therapies in pipeline
To improve Duration of Effect

Continuous dopamine stimulation
• Accordian Pill: Delayed release mechanism so slow onset. Taking this twice daily = 4 doses of IR, with 2 hours improved on time and less dyskinesias

For sudden off symptoms
• Sublingual Apomorphine
• Inhaled Levodopa

Neuroprotection
• Isradipine (CCB)
• Studying Uric Acid (causes gout) as individuals with higher urate levels are less likely to develop PD (?antioxidant effect)
What does the future hold

• It is a time of optimism, as so much is going on in research, and I am hopeful that soon we will have neuro-protective medications and a way to identify people at risk sooner, to help prevent progression.

• The most important thing you can do is to keep a positive outlook, stay engaged, eat a healthy diet and exercise
CASE STUDY 1

- 65 year old right handed man
- Noted tremor of right hand when driving and holding newspaper, as well as at rest
- Right shoulder pain for 6 months
- Constipation and reduced smell
- Exam: “poker face”, reduced eye blink, soft voice, mild ‘rigidity’ at right elbow, low frequency tremor of right hand at rest that re-appears with arms extended, small movements of right hand and slower than left hand, reduced right arm swing
- Walking is good with no loss of balance and symptoms not interfering in QOL
CASE STUDY 1

- He is dx with tremor predominant idiopathic parkinson disease, based on the cardinal motor symptoms (slowness, rigidity and tremor) with multiple supportive criteria precede by non-motor symptoms (constipation, reduced smell).
- Because his symptoms are mild and not interfering with QOL, he elects to not start any medications. Advised to start rigorous exercise 30 minutes/day and focus on stretching, core strength and ROM of arms.
- If tremor is only thing bothering him, he could try trihexyphenidyl, especially given young age.
CASE STUDY 1

• He returns to the office in 6 months
• Tremor has increased and he has noticed his walking is slower, and he sometimes stumbles. Still not swinging right arm and manual dexterity is not as good
CASE STUDY 1

• Discussed starting medication and reviewed options. He is young and still working, so starting levodopa/carbidopa 25/100 three times daily (empty stomach)
• Referred for physical therapy
• Reminded to exercise regularly
CASE STUDY 1

• Returned in 6 months and says the medication has helped with the slowness and stiffness as well as manual dexterity, but tremor still prominent and not responsive

• He completed physical therapy (LSVT BIG) and says helpful

• Started him on a low dose of trihexyphenidyl
CASE STUDY 1

• Returned in 6 months and says the medication has helped with the slowness and stiffness as well as manual dexterity, and tremor improved.
• He continues to exercise 4 days per week.
• Remained well controlled for one year and then returns with increasing slowness and stiffness.
CASE STUDY 1

• So 2 ½ years post diagnosis and taking 25/100 levodopa/carbidopa 3 times daily every 6 hours

• After discussion, he notes the increased slowness/stiffness occurred about one hour prior to next dose and otherwise doing well

• Interval shorted to every 5 hours and continues on same dose of levodopa/carbidopa and trihexyphenydyil 1mg three times daily
CASE STUDY 1

• One year later (3 ½ years post diagnosis) he returns with worsening symptoms overall, wearing off at 4 hours, and has had one fall. Voice softer and speech not as clear. Occasionally will choke on food

• Increased levodopa/carbidopa to 1 ½ to 2 tablets four times daily at 4 hour interval

• Continue to exercise and referred back to physical therapy and added occupational and speech therapy (LSVT LOUD)
CASE STUDY 1

- 6 years post diagnosis continues taking 2 tablets 25/100 levodopa/carbidopa four times daily plus trihex and now wearing off at 3 hours. He has difficulty rolling over in bed and is very slow first thing in the morning before the medication starts working. He has also noted some drooling
CASE STUDY 1

- Continue levodopa/carbidopa 2 tablets four times daily and adding rasagiline 1mg once daily to extend duration of levodopa/carbidopa. Reduce interval to 3 ½ hours four times daily.
- Added CR levodopa/carbidopa 50/200 at bedtime.
- Continues with trihexyphenyldil.
- Chew gum or suck on sugar free candy to help stimulate swallowing excess saliva (reduce drooling). Advised if not effective we would try 1% atropine drops under tongue.
CASE STUDY 1

10 years post diagnosis (75 years old), dose of levodopa/carbidopa is increased to 3 tablets 25/100 four times daily at 3 ½ hour intervals and he is having a lot of fluctuations in effectiveness. He is also having troublesome dyskinesias at peak dose along with some confusion and worsening constipation
CASE STUDY 1

- Discussed option of trial of Rytary (combination of IR and CR levodopa/carbidopa) and adding amantadine for dyskinesias
- Trihexyphenyldil d/c based on potential cognitive side effects and worsening constipation (not controlled with daily mirapex)
- He elects to switch to rytary and sees improvement for the next two years, but fluctuations increase again and dyskinesias have increased as well along with worsening resting tremor
- Discussed DBS vs duopa and workup required
CASE STUDY 2

• 54 year old woman with tremor of left hand (she is right handed). Works with her hands and has noted mild changes in dexterity of left hand. Her left leg is ‘jumpy’ at night with urge to move it and sometimes talks in her sleep and acts out dreams

• On exam, there is mild ‘poker face’ with intermittent tremor of left hand. Left hand movements a little slower. Reduced arm swing with walking but good stride length and speed
CASE STUDY 2

• Diagnosed with Parkinson disease
• Based on mild symptoms discussed options of medications (levodopa/carbidopa, dopamine agonists, rasagiline, nothing)
• She elects to start with rasagiline and will start exercising more
• Also advised to start melatonin to see if sleep improves, and ferritin levels checked (deficiency can cause RLS type symptoms)
CASE STUDY 2

- 6 month f/u: Doing well on rasagiline and exercise, but mild progression of tremor and slowness
- Melatonin 5mg taken 1 hour prior to bedtime helps with sleeping
- Continues to have Restless legs at bedtime that make falling asleep more difficult at time and ferritin levels normal
  - Confirmed not taking antidepressants which can worsen this
- Will start pramipexole XR 0.375mg bedtime
  - Will help RLS plus PD symptoms
- Referred for PT/OT
CASE STUDY 2

• 3 years later she is taking pramipexole 2.25mg bedtime plus rasagiline and continues to exercise regularly

• She has noticed that she is having obsessive thoughts and buying items she would normally not buy, but otherwise controlled

• Having more difficult falling asleep, and some problems with depression and anxiety
CASE STUDY 2

- She is having side effects of the pramipexole, so this will be tapered off
- She will start levodopa/carbidopa 25/100 three times daily at 5 hour intervals and continue on rasagiline
- Continue on melatonin
- Start Trazodone to help with sleep and is an anti-depressant
CASE STUDY 2

- She is having side effects of the pramipexole, so this will be tapered off.
- She will start levodopa/carbidopa 25/100 three times daily at 5 hour intervals and continue on rasagiline.
- Continue on melatonin.
- Start Trazodone to help with sleep and is an anti-depressant.
CASE STUDY 2

• 15 years after diagnosis (69yo) she is taking levodopa/carbidopa 25/100, 2 1/2 tablets four times daily at 4 hour intervals
• Continues on rasagiline
• No wearing off or fluctuations but has started having hallucinations and worried about her memory
  • If she were still on a dopamine agonist, would stop that initially
• Start pimavanserin (nuplazid) and informed it can take 4-5 weeks to see improvement
• Referred to neuropsychology for assessment of memory
CASE STUDY 2

• 15 years after diagnosis (69yo) she is taking levodopa/carbidopa 25/100, 2 1/2 tablets four times daily at 4 hour intervals
• Continues on rasagiline
• Pimavanserin (nuplazid) has improved hallucinations
• Neuropsychology assessment completed and noted she has symptoms for Parkinson disease with mild cognitive impairment and likely early Parkinson dementia
• Started on rivastigmine with improvement
CASE STUDY 2

- 20 years after diagnosis (79yo) she is taking levodopa/carbidopa 25/100, 3 tablets four times daily at 3 hour intervals with fluctuations
- Continues on rasagiline
- pimavanserin (nuplazid) has continued to improve hallucinations
- Continues on rivastigmine with improvement
- Discussed options. Rytary too expensive and does not qualify for DBS based on cognitive decline.
- She is considering duopa. However, it was determined that the fluctuations were being caused by inconsistent intervals, so after having someone come in and help with medication management and taking on empty stomach, the fluctuations improved