

Treatment of Parkinson disease: lessons I've learned from cases

Ali Samii, M.D.

Professor of Neurology

University of Washington School of Medicine

VA Puget Sound Health Care System

Epidemiology

- 0.3 percent of the general population
- 1% of the population over the age of 60
- 500,000-1,000,000 persons in the U.S.
- Men slightly more affected than women
- Mean age of onset is ~ 60
- Young-onset PD: symptom onset before age 50
 - 10% of PD patients are young-onset

Samii, Nutt, Ransom. Lancet 2004; 363(9423): 1783-93

Cardinal Signs of PD

- Asymmetric resting tremor (UEs>LEs)
 - 70% of PD patients have tremor as first symptom
 - typically pill rolling
- Asymmetric cogwheel rigidity
 - enhanced by contralateral motor task performance
- Asymmetric bradykinesia (slowness of movement)
- Postural instability
 - least specific cardinal sign of PD
 - usually absent in early stages of PD

Non-motor features of early PD

- May precede cardinal motor features by several years
- Rapid Eye Movement (REM) Sleep Behavior disorder
- Hyposmia (reduced sense of smell)
- Depression, anxiety, and mild cognitive problems
- Dysautonomia:
 - constipation
 - reduced heart rate variability
 - sexual dysfunction
 - bladder urgency

Park A and Stacy M. J Neurol. 2009;256 (Suppl 3):293-8

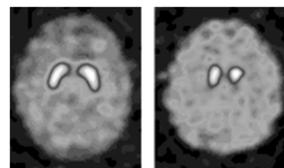
PD Diagnostic Criteria

- clinically possible PD:
 - any one of resting tremor, rigidity, or bradykinesia
- clinically probable PD:
 - any two of resting tremor, rigidity, or bradykinesia, especially if asymmetric
- clinically definite PD:
 - clinically probable PD
 - and good response to anti-parkinson medications

Samii, Nutt, Ransom. Lancet 2004; 363(9423): 1783-93

SPECT DaTSCAN

- Dopamine transporter scan
- SPECT DaTSCAN (Ioflupane-¹²³I)
- FDA-approved for differentiating healthy state and essential tremor from Parkinsonian syndromes
- Not helpful for differentiating Parkinson disease from Parkinson Plus syndromes



Normal

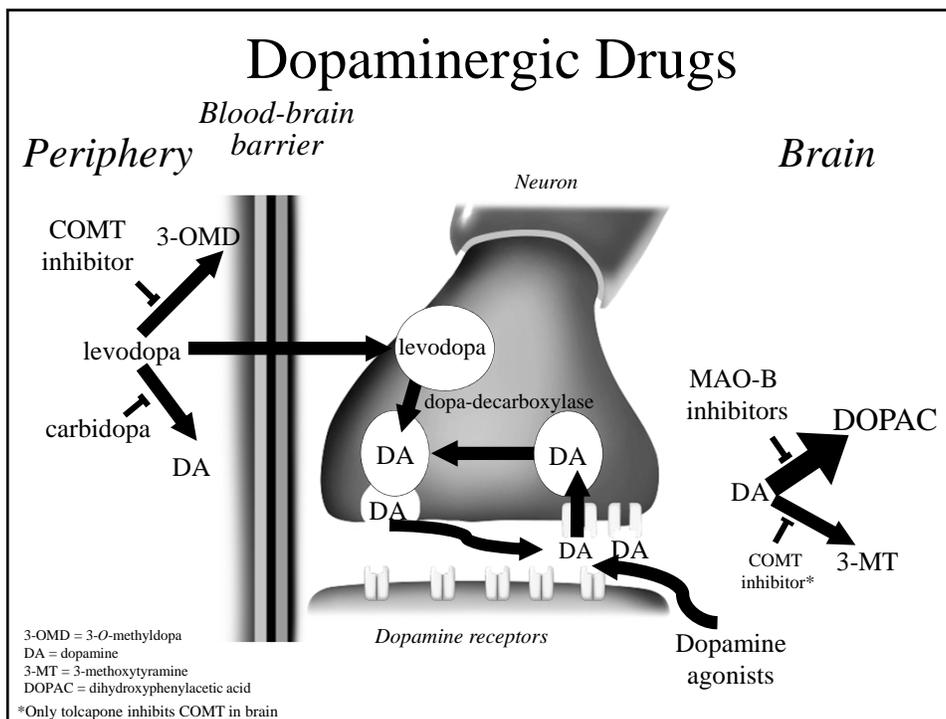
PD

Pharmacotherapy

- Some believe that treatment should start at the onset of diagnosis, while others suggest treatment when “functional impairment” is present

Functional Impairment

- Impairment in activities of daily living
- Impairment in carrying out employment and potential for job loss
- Painful dystonia or rigidity
- Onset of frozen joint syndrome
- Disturbance of gait and balance
- Social embarrassment because of tremor



Carbidopa/levodopa

- Still the most effective PD drug
- Various combinations of carbidopa/levodopa:
 - 25/100
 - 25/250
 - 10/100
 - 25/100 CR
 - 50/200 CR
- Many generic versions available
- Levodopa in the CR version is 30% less absorbed than regular version

Problems with carbidopa/levodopa

- Short half-life
- End-of-dose wearing off
- Fluctuations between off and on states
- Dietary protein may limit levodopa absorption
- Dyskinesia (40% at 5 years, 80% at 10 years)
- Side effects:
 - nausea alleviated by additional carbidopa (Lodosyn)
 - drop in blood pressure and dizziness
 - drowsiness, but less so than dopamine agonists

COMT Inhibitors

- Comtan (entacapone) 200 mg used with each dose of carbidopa/levodopa up to 6 times daily
- Blocks COMT which breaks down levodopa, thereby increasing the duration of action of levodopa and increasing levodopa levels in the blood
- Helps alleviate end-of-dose wearing off
- Stalevo is a combination of carbidopa/levodopa/entacapone all in one pill with many available doses
- Entacapone makes urine bright orange, may cause diarrhea, and may exacerbate levodopa's side effects like dyskinesia
- Tasmartol (tolcapone) 100 mg is more potent, but rarely used because it can cause liver damage and requires frequent blood tests to monitor liver function

Dopamine agonists

- Agonists bind directly on dopamine receptors
- Longer half-life (less fluctuations) than levodopa
- Less potent than levodopa but more potent than MAO-B inhibitors
- Side effects:
 - Nausea/vomiting and leg edema
 - Dizziness and low blood pressure
 - Somnolence and sleep attacks
 - Hallucinations and psychosis
 - Compulsive gambling and disinhibited behavior

Dopamine agonists

- Pramipexole (Mirapex) and ropinirole (Requip) are oral
- Rotigotine (Neupro patch) absorbed through the skin
- Effective for both early and advanced PD
- Less dyskinesia than levodopa
- Allow for lower dose of levodopa
- Dose ratio:
 - 1 mg pramipexole ~ 4 mg ropinirole ~ 4 mg rotigotine
- Ropinirole and pramipexole available in generic
- Once daily Mirapex ER and Requip XL available
- Apokyn (apomorphine) s.c. injection for quick rescue of severe off period

Monoamine Oxidase-B Inhibitors

- Used in early and advanced PD
- Disease modification/neuroprotection unproven
- Selegiline (generic)
 - 5 mg twice daily
 - stimulant byproducts may help alertness
 - second dose no later than noon
- Rasagiline (Azilect):
 - 1 mg once daily
 - no amphetamine byproducts
- Zelapar (orally disintegrating selegiline) 1.25 mg or 2.5 mg once daily as adjunct therapy

Amantadine

- Used as antiviral drug in early 1960s
- Used in treating PD since late 1960s
- Mechanism of action not entirely clear
- Inhibits a receptor in the brain called NMDA
- Sometimes used in early PD with mild benefit
- Now more often used to reduce dyskinesia caused by levodopa in more advanced PD

Memory Enhancing Drugs

- Cholinesterase Inhibitors:
 - block the breakdown of acetylcholine in the brain
 - rivastigmine (Exelon)
 - available in oral and patch form
 - FDA-approved for dementia associated with PD
 - galantamine (Razadyne)
 - donepezil (Aricept)
- NMDA receptor blocker:
 - memantine (Namenda)
 - usually used as add-on to cholinesterase inhibitor

Medications for Hallucination and REM Behavior Disorder

- Atypical antipsychotics
 - safest one in PD is quetiapine (Seroquel) at low doses of 25-75 mg daily
 - clozapine (Clozaril) is rarely used because of bone marrow suppression and requires frequent blood monitoring
- REM behavior disorder
 - clonazepam (Klonopin) at 0.5 mg to 1 mg
 - melatonin at 3 mg or higher

Recent New Drugs

- Rytary: new version of carbidopa/levodopa that lasts longer than currently available versions and may allow fewer doses per day
- Duodopa intestinal gel delivers continuous carbidopa/levodopa directly via a pump attached to a surgically placed tube into the small intestine

Deep brain stimulation

- Thalamic DBS improves contralateral tremor
- Pallidal (GPi) DBS
 - improves most motor symptoms
 - less medication reduction compared to STN
- Subthalamic nucleus (STN) DBS
 - improves most motor symptoms
 - allows reduction in anti-PD meds
- Multi-center randomized study of bilateral GPi vs. bilateral STN stimulation:
 - First phase (best medical therapy vs. surgery) showed significant benefit but more adverse effects with surgery
 - Second phase (STN vs. GPi) showed equal efficacy but slightly more cognitive and mood problems with STN compared to GPi but more medication reduction with STN

Weaver et al. JAMA 2009;301(1):63-73

Follett et al. NEJM 2010; 362(22):2077-91

Who is a candidate for deep brain stimulation surgery?

- Improvement with medications but doses are maximized and cannot be increased because of side effects
- Disabling off periods or dyskinesias > 3 hours daily
- No serious medical conditions
- No serious memory or psychiatric problems
- Preferably less than 75 years old
- Willing to return for frequent programming sessions
- Have realistic expectations from surgery

Case 1

- 74 y.o. woman with 6 months of LUE tremor
- PMHx: CAD, COPD, arthritis
- O/E: obese, reduced facial animation, LUE resting tremor, bilateral wrist cogwheel rigidity (L>R), mild postural instability
- Sinemet CR 50/200 1/2 qid improved tremor and mobility, but 1 qid caused nausea
- Settled on Sinemet CR 50/200 tid at 5 hr intervals with non-protein-rich snack

Case 1 lessons:

- In older patients with co-morbid conditions, it is safer to begin treatment with levodopa
- Taking anti-Parkinson meds with non-protein-rich meals can help reduce drug-induced nausea

Case 2

- 46 y.o. right-handed woman who presented for evaluation of left hemi-dystonia mostly involving the foot
- 6 months of left foot inversion, curling of left toes, clumsiness of the left upper extremity
- MRI: tortuous left vertebral artery, indenting brainstem, hence patient referred to neurosurgery
- Neurosurgery referred patient to neurology for management of dystonia

Case 2 (cont' d)

- O/E: LUE cogwheel rigidity, left foot dystonia, slow left finger tapping and alternating movements, but no tremor
- Started on dopamine agonist and dose titrated without side effects
- Motor improvement with resolution of left foot dystonia and improved mobility
- Diagnosis of Parkinson disease was made

Case 2 lessons:

- Tortuous vessels are common findings on MRI and do not necessarily cause symptoms
- Dystonia (especially of the foot) can be a presenting sign in Parkinson disease
- In young healthy patients, can begin treatment with dopamine agonist or MAO-B inhibitor
- Medication responsiveness is a key feature of clinically-definite PD

Case 3

- 71 y.o. woman with 4 months of LUE tremor when lifting heavy objects and LUE clumsiness
- O/E: LUE tremor at rest and when holding objects, cogwheel rigidity at L wrist + L elbow, reduced L arm swing during ambulation
- Patient reported no response to Sinemet CR 50/200 1/2 qid
- Dose could not be increased because of nausea even when Sinemet was taken with food

Case 3 (cont' d)

- Tapering of Sinemet led to worsening of tremor and LUE clumsiness
- Resumed Sinemet CR this time with Lodosyn (extra carbidopa) 25 mg tabs with each dose of Sinemet
- Significantly improved motor symptoms on Sinemet CR 50/200 qid with no nausea on Lodosyn

Case 3 lessons:

- Action tremor may accompany resting tremor in Parkinson disease
- Some patients need a high dose of levodopa to initially respond: some suggest that at least 1,000 mg of immediate-release levodopa must be tried before concluding “medication failure”
- Tapering meds looking for motor deterioration can be more sensitive than dose increase in establishing medication responsiveness
- Lodosyn provides extra carbidopa (25 mg) and helps reduce levodopa-induced nausea

Case 4

- 62 y.o. man with one yr hx of RUE tremor
- 30 yr hx of mild essential tremor when anxious
- Tremor spread over 1 yr to head and all 4 limbs
- 4 yr hx of anxiety, depression, and palpitations
- O/E: resting and action tremor R>L, cogwheel rigidity, masked face, slow gait, and micrographia
- No improvement on Sinemet 25/100 2 tabs tid
- No deterioration after sudden cessation of Sinemet

Case 4 (cont' d)

- Pt was taking large amounts of protein in form of meat and dairy with each dose of Sinemet
- Sinemet re-trial:
 - titrate CR 50/200 1.5 tabs qid (1200 mg)
 - reduce protein intake and change timing of Sinemet
- Results:
 - improvement in tremor and mobility on Sinemet CR 50/200 6 tabs daily
 - started riding bicycle to UW campus again

Case 4 lessons:

- Essential tremor and Parkinson disease can occur in the same person
- Some patients need a higher dose of anti-parkinson meds to initially respond
- Protein intake may reduce the efficacy of levodopa because amino acids compete with levodopa in absorption and crossing the blood brain barrier

Case 5

- 36 y.o. man congenital hypoparathyroidism with hx of bilateral tremor, L>R
- O/E: resting and action tremor, rigidity and bradykinesia, L>R
- Sinemet CR 50/200 1/2 qid improved motor sx
- Presented to ER with neck dystonia in “medication off” period: one dose of regular Sinemet 25/100 resolved cervical dystonia
- Increase in Sinemet CR and adding pramipexole led to further improvement in “wearing off”

Case 5 (cont' d)

- One year later patient became psychotic with visual hallucinations and paranoid delusions
- Admitted to inpatient psychiatric service
- Pramipexole was stopped
- Quetiapine was added and the dose was titrated to 100 mg bid
- Bradykinesia worsened without pramipexole and addition of quetiapine
- Quetiapine reduced to 50 mg bid
- Settled on Sinemet CR 50/200 qid and quetiapine 50 mg bid

Case 5 lessons:

- Dystonia occurs often during OFF periods, especially in early morning before the first dose
- Dopamine agonists added to levodopa can help relieve wearing OFF
- Dopamine agonists have a higher tendency than levodopa to induce psychosis
- Quetiapine even at low doses is effective in reducing psychosis
- Quetiapine may still worsen motor symptoms of Parkinson disease

Case 6

- 47 y.o. man with young-onset PD transferring care:
 - Sinemet CR 50/200 t.i.d. (7:00, 13:00, 19:00)
 - Sinemet regular 25/100 5X/day at 3 hr intervals
- Main complaint: end-of-dose wearing off
- Medication changes:
 - Sinemet CR 50/200 1.5 tabs qid
 - Sinemet regular 25/100 qam for jump start
 - Added entacapone 200 mg qid with good results

Case 6 lessons:

- Levodopa in Sinemet CR is 30% less bio-available than in immediate-release Sinemet, so higher of levodopa when switching to CR
- Use immediate release Sinemet in a.m. for “jump start” and as needed for added boost
- Some patients can't do without the immediate-release Sinemet and like the “high” from it
- Comtan (entacapone) increases levodopa levels and helps relieve end-of-dose wearing off

Case 7

- 65 y.o. woman with hx of PD for a decade
- Transferring care to UWMC
- Severe disabling dyskinesia (almost all day)
- Meds:
 - Sinemet regular 25/100 one tablet in am
 - Sinemet CR 50/200 two tablets daily (1-1/2-1/2)
 - Tasmar (tolcapone) 100 mg tid with liver enzyme monitoring
 - Requip 2 mg tid (6 mg/day)

Case 7 (cont' d)

- Changes in meds:
 - D/C Tasmar
 - No change in overall Sinemet CR (50/200 2 tabs daily) but divide it over 4 doses (1/2 tab qid)
 - No change in regular Sinemet (one 25/100 in am)
 - Double Requip to 3 mg qid (12 mg/day)
- Results:
 - significant reduction in dyskinesia
 - no worsening of bradykinesia
 - no need for LFT monitoring (since Tasmar stopped)

Case 7 lessons:

- Tasmar (tolcapone) is a COMT inhibitor more potent than Comtan (entacapone)
 - fatal liver failure reported with Tasmar requiring liver function tests (no longer available in many countries)
- Try more even delivery of anti-parkinson meds
- Dopamine agonists are less likely to induce dyskinesias:
 - Lower levodopa doses (in this case by eliminating Tasmar)
 - Compensate for reduced levodopa by increasing dose of dopamine agonist

Case 8

- 55 y.o. with 17 yr hx of PD (young onset)
- Sinemet regular 25/100: 2 tabs q 90 min (20/day)
- CC: severe motor fluctuations
 - more than 4 hrs/day in OFF state (predictable end of dose wearing off and unpredictable OFF periods)
 - the remainder in the ON/dyskinetic state
 - painful dyskinesia requiring analgesics
- Requip trial: severe dizziness, nausea, and diaphoresis
- Switch to Sinemet CR: unpredictable and severe wearing off

Case 8 (cont' d)

- added entacapone 200 mg 7 tabs/day
- reduced Sinemet 25/100 to 2 tabs 7X/day (14/d)
- increased inter-dose interval to 2.5-3 hrs
- improved wearing off (less than 3hrs/day in OFF state)
- still had moderate to severe dyskinesia
- bilateral subthalamic nucleus (STN) stimulation
 - marked improvement in motor fluctuations
 - reduced Sinemet and entacapone from 7 doses to 4 doses daily
 - marked reduction in dyskinesia

Case 8 lessons:

- COMT inhibitors can alleviate end-of-dose wearing off but can exacerbate dyskinesia
- Bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) improves motor symptoms may allow reduced medication doses
- Bilateral internal globus pallidus (GPi) stimulation also improves motor symptoms but does not result in as much medication reduction
- Young (under 75), healthy, non-demented patients, with motor fluctuations and severe dyskinesia are good candidates for DBS surgery

Case 9

- 69 y.o. man from Punjab
- Sx onset unclear, possibly mid-1990s
- Treatment started shortly after arrival in US:
 - Sinemet 25/100 tid
- O/E:
 - severe generalized rigidity/bradykinesia
 - marked impairment of balance
 - cognition difficult to test b/o illiteracy and language barrier

Case 9 (cont' d)

- Switched to Sinemet CR 50/200 and dose titrated to 1.5 tabs qid (6 tabs/day) resulting in improved mobility and balance
- Admitted for failure to thrive with severe esophageal strictures requiring dilatation
- PEG tube placed and patient switched back to immediate-release Sinemet (crushed)
- Developed nausea, orthostatic hypotension, dyskinesia, and hallucinations

Case 9 (cont' d)

- Nausea improved with esophageal dilatation and Lodosyn
- Placed on Florinef but developed a rash
- Midodrine improved orthostatic hypotension
- Dyskinesia improved with:
 - reduction in Sinemet
 - addition of pramipexole (0.25 mg qid)
- Hallucinations developed in setting of hyponatremia (Na=118) with citalopram (SIADH)
- Hallucinations persisted after Na correction

Case 9 (cont' d)

- Quetiapine 12.5 mg bid worsened motor sx
- Pt received Haldol 1 mg in ER (for CT scan)
 - Haldol 1 mg led to severe rigidity requiring admission
- Clozapine started and titrated to 12.5 mg bid
 - significant reduction in hallucinations
 - no deterioration of motor sx
 - weekly CBC for 6 months, then q 2 weeks

Case 9 lessons:

- When delivering Sinemet via NG or PEG tubes, use immediate release (crushing Sinemet CR turns it into immediate-release)
- For treatment of hypotension:
 - Florinef up to 0.3 mg daily: mineralcorticoid
 - Midodrine up to 10 mg tid: vasoconstrictor
- Dopamine agonists are more likely to cause hallucinations and less likely to cause dyskinesia
- Metabolic derangement exacerbates hallucination
- PD patients are extremely sensitive to potent neuroleptics like Haldol
- Clozapine: last resort to treat hallucinations

Case 10

- 52 yo man with motor PD onset in at age 45 (R bradykinesia), started on ropinirole which caused vomiting
- Switched to carbidopa/levodopa CR 50/200 and entacapone which was titrated over years to 5 times daily
- Pramipexole was added with dose titration to 1.5 mg 5X/day
- Developed gambling and hypersexual behavior (pornography and placing ads on singles websites while married), which did not improve until pramipexole was completely stopped
- Bilateral STN DBS which improved motor fluctuations and dyskinesia
- Carbidopa/levodopa/entacapone dose reduction after DBS

Case 10 lessons:

- Some patients tolerate one dopamine agonist better than the others
- Impulse control disorder occurs more often in patients taking higher doses of dopamine agonists, younger male patients with pre-morbid history of novelty seeking behavior
- Dopamine agonist may have to be stopped entirely before impulse control disorder improves
- Always ask family members and caregivers about impulse control disorder, as patient may not recognize behavior or be willing to talk about it
- Bilateral STN DBS surgery tends to allow medication dose reduction