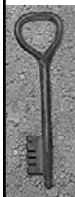




Management of Parkinson's Disease

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Cardinal Features of Parkinson's

- ◆ Tremor
 - Unilateral, at rest, most commonly in hands
- ◆ Rigidity
 - “cog-wheel”
- ◆ Akinesia and bradykinesia
- ◆ Postural instability
 - Most disabling problem of PD
 - Pull test



Other Parkinson's Symptoms

- ◆ Micrographia (small handwriting)
- ◆ Hypomimia (decreased facial animation)
- ◆ Decreased blink rate
- ◆ Diminished arm swing while walking
- ◆ Shuffling, festinating gait
- ◆ Hypophonia (soft or indistinct speech)
- ◆ Decreased dexterity in everyday activities
- ◆ *Diagnosis is made by clinical observation



Drug Induced Parkinson's

- ◆ Antipsychotics
- ◆ Antiemetics
 - Metoclopramide
 - Prochlorperazine
- ◆ Other
 - Reserpine, alpha-methyl dopa



Marcia: Part I

- ◆ Marcia is a 66 yo director of volunteer services at the local hospital. She notes that she has slowed down to an inconvenient degree. As a result, she requires 25 minutes to dress each morning and she can no longer prepare her breakfast quickly enough to get to work on time. Friends have noted the development of her impassive face, too quiet voice and slow, small-stepped gait.

Ham RJ. Parkinson's Disease. Chapter 47 in Ham RJ, Sloane PD, Warshaw GA, eds. Primary Care Geriatrics: A Case Based Approach, 4th edition. St. Louis, MO: Mosby, 1999. Pages 605-614.



Marcia: Part II

- ◆ PE reveals convincing signs of parkinsonism. Not only is she bradykinetic, she also has a forward-bent posture and tends to fall backward, walks with a diminished arm swing and has little facial animation. There is a hint of cogwheel-like resistance to passive movement of her arms but little tremor.

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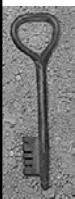
Marcia: Discussion Questions

- ◆ What Parkinson features can you identify?
- ◆ Should drug therapy be initiated?
- ◆ What agent should be chosen?



To Access Latest Parkinson's Treatment Guidelines

- ◆ www.neurology.org/content/vol66/issue7



Approaching Treatment of PD

- ◆ Mimic dopamine
- ◆ Increase dopamine
- ◆ Decrease acetylcholine
 - The dopamine/acetylcholine “see-saw”



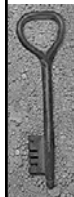
Anticholinergic Medications

- ◆ Block acetylcholine
- ◆ May be effective against tremor; no benefit for other PD symptoms
- ◆ Bzotropine (Cogentin)
 - Initiate at 0.5 mg @HS
 - May increase by 0.5 mg at 5-6 day intervals up to 6 mg/day
 - Must also taper to d/c
- ◆ **USE WITH CAUTION IN THE ELDERLY**



Amantadine (Symmetrel)

- ◆ NMDA-receptor antagonist, blocks glutamate, promotes DA, blocks ACh
- ◆ May be beneficial as monotherapy in mild PD
- ◆ May reduce levodopa-induced dyskinesia
- ◆ Usual dose: 100 mg BID up to 400 mg/day
 - Must titrate up/down
 - Half dose in elderly patients
 - Must be adjusted for renal function



Selegiline (Eldepryl) (Zelapar)

- ◆ MAO-B inhibitor: prevents central degradation of dopamine
- ◆ Monotherapy: may delay need for levodopa
- ◆ Adjunctive therapy with Sinemet
 - Increases peak effect of levodopa
 - Worsens dyskinesias and psychosis
 - May be able to reduce levodopa dose by as much as 50%



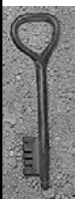
Selegiline (Eldepryl) (Zelapar)

- ◆ Zelapar is oral disintegrating tablet
- ◆ Dosing
 - 5 mg BID with breakfast and lunch
 - Do not give doses later in day (amphetamine metabolites)
 - Specificity for MAO-B lost at doses >10 mg/day



Rasagiline (Azilect)

- ◆ Second-generation MAO-B inhibitor
 - More selective and more potent than selegiline
- ◆ Diarrhea, weight loss, hallucinations, rash
- ◆ CYP1A2 interactions (Cipro)
- ◆ Dose: 0.5 mg – 1 mg daily
- ◆ Place in therapy
 - Monotherapy in early PD
 - Adjunct therapy for reducing “off” time



Marcia: Part III

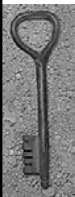
- ◆ Marcia is started on: rasagiline 0.5 mg daily, then 1 mg daily
- ◆ She shows improvement and continues working and starts a Parkinson’s support group.
- ◆ Eighteen months later her bradykinesia has increased and her effectiveness at work is impaired. She asks if a more effective treatment is available.

Ham RJ. Parkinson’s Disease. Chapter 47 in Ham RJ, Sloane PD, Warshaw GA, eds. *Primary Care Geriatrics: A Case Based Approach*, 4th edition. St. Louis, MO: Mosby, 1999. Pages 605-614



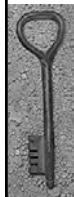
Carbidopa/Levodopa (Sinemet)

- ◆ Mainstay of PD therapy since 1960s
- ◆ Administered in combination with carbidopa
 - Peripheral decarboxylase inhibitor
 - Increases effectiveness of levodopa
 - Decreases SE of N/V and orthostatic hypotension associated with levodopa
 - At least 75 mg daily is needed for prevention of peripheral metabolism of levodopa



Carbidopa/Levodopa (Sinemet)

- ◆ Most common side effects are: ortho hypo, dizziness, nausea, hallucinations
- ◆ Must titrate up slowly to achieve effective dose while minimizing adverse effects



Carbidopa/Levodopa (Sinemet CR)

- ◆ Controlled-release formulation
- ◆ Decreased bioavailability
 - May need to increase dose as much as 30% when switching from IR to CR
- ◆ Immediate release carbidopa/levodopa may be added in the morning



Carbidopa/Levodopa (Parcopa)

- ◆ Rapidly dissolving oral formulation
- ◆ Onset: 5-10 minutes
- ◆ Benefits: patients who need early morning dose, have strict dosing schedules, or who have swallowing difficulties
- ◆ Contains phenylalanine
- ◆ Available: 10mg/100 mg, 25mg/100mg, 25mg/250mg
- ◆ Tablets CAN be split



Marcia: Part IV

- ◆ Now that her symptoms have progressed, the patient is started on Sinemet. She experiences some stomach upset with the Sinemet, which slows titration, but as the dose is increased, she feels better, speedier and more effective in her movements. She remains working, sustained on Sinemet, until her retirement at age 70.

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Levodopa Therapy Complications

- ◆ Up to 75% of patients develop these
- ◆ Motor fluctuations
 - “Wearing off”
 - “On/Off”
- ◆ Dyskinesias
- ◆ Dystonias
- ◆ Psychosis



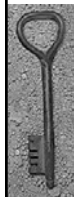
Motor Fluctuations

- ◆ “Wearing Off”
 - Increasing loss of functional dopaminergic neurons
 - Motor symptoms return before next dose is due
 - Switch to controlled-release levodopa or give doses more often – most recent guidelines do not favor this option
 - Add or increase dopamine agonist
 - Add COMT inhibitor or MAO-B inhibitor
- ◆ “On/Off”
 - Fluctuation of “On” to “Off” periods are unpredictable and often a relationship to dose cannot be established



Dyskinesias

- ◆ Choreiform abnormal involuntary movements of neck, trunk, upper extremities
- ◆ Associated with peak antiparkinsonian benefit
- ◆ Smaller, more frequent doses of levodopa
- ◆ Use of controlled-release product
- ◆ Addition of dopamine agonist



Dystonias

- ◆ Sustained muscle contractions or abnormal postures
 - Lower extremities
 - Early morning hours
- ◆ Bedtime controlled-release levodopa
- ◆ Parcopa
- ◆ Baclofen
- ◆ Botox



Akathisia

- ◆ AKA: restless leg syndrome
- ◆ Nighttime dopaminergic medications
- ◆ Clonazepam
- ◆ Propranolol



Psychosis

- ◆ Levodopa can affect other dopamine pathways, resulting in psychiatric symptoms
 - Delirium, agitation, paranoia, delusions, hallucinations
- ◆ Occurs more frequently in older patients
- ◆ Rule out drug-induced causes
- ◆ Reduce levodopa
- ◆ Add low-dose quetiapine (12.5 mg @HS)



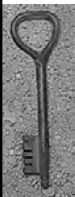
Questions for Patients

- ◆ Ask these important questions before adjusting the dose or timing of medications.
- ◆ When did the dose start to work and how long did it last?
- ◆ How did you feel just before the dose, and during the dosing period?



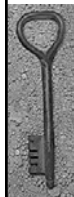
Apomorphine (Apokyn)

- ◆ Dopamine agonist approved for the acute, intermittent treatment of “off” episodes
- ◆ Onset = 10 minutes Duration = 60 minutes
- ◆ 2-6 mg subcutaneous injection, never IV
- ◆ May repeat up to 5 times a day PRN
- ◆ Caution patients with sulfite allergy



Apomorphine (Apokyn)

- ◆ Common side effects: injection site reaction, N/V(SIGNIFICANT), dizziness, sedation, hallucinations, peripheral edema, sexual stimulation
- ◆ Trimethobenzamide (Tigan) is only approved agent for nausea associated with Apokyn



Apomorphine (Apokyn)





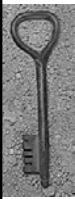
Dopamine Agonist Agents

- ◆ Adjunct or alternative to levodopa
- ◆ May be able to reduce levodopa dose 20-30% when adding dopamine agonist
- ◆ DO NOT depend on functioning presynaptic neurons for their pharmacologic activity



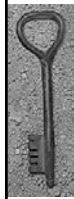
Ropinirole (Requip)

- ◆ Extensive liver metabolism
- ◆ CYP450 1A2 drug interactions
 - Smoking will increase clearance
 - Cipro



Ropinirole (Requip) Dosing

- ◆ Week 1: 0.25 mg TID
- ◆ Week 2: 0.5 mg TID
- ◆ Week 3: 0.75 mg TID
- ◆ Week 4: 1 mg TID, then increase as needed by 0.15 mg/d weekly up to 9 mg/d, then by up to 3 mg/d to a max of 24 mg/d
- ◆ Usual dose is 3-24 mg/d given TID



Pramipexole (Mirapex)

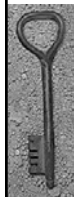
- ◆ Extensive renal elimination
 - Use decreased dose when ClCr <60 ml/min
- ◆ Initiate at 0.125 mg TID
- ◆ Increase every 5 to 7 days as tolerated
- ◆ Usual dose = 0.5 – 1.5 mg TID



Rotigotine (Neupro) Patch

- ◆ Three strengths: 2 mg, 4 mg, 6 mg
- ◆ Initiate at 2 mg and increase weekly
- ◆ Minimum effective dose in trials 4 mg
- ◆ No known significant drug interactions
- ◆ May not be appreciable differences from pramipexole in safety or efficacy¹
- ◆ ****March 2008 Recall****

1. Neurology 2007;65:13-20.



Proposed Dosage Conversion

	Daily Dose (mg)			
Ropinirole (Requip)	2	4	6	8-9
Pramipexole (Mirapex)	0.5	1	1.5	2
Rotigotine (Neupro)	2	4	6	8

Nausieda P, Patton J, Neilson S, et al. Tolerability of switching from an oral dopamine agonist to transdermal Rotigotine in Parkinson's disease [poster]. Presented at the College of Psychiatric and Neurologic Pharmacists 2007 Annual Meeting, April 15-18, 2007, Colorado Springs, CO.



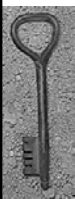
Dopamine Agonist Side Effects

- ◆ Nausea (18-36%)
- ◆ Confusion, hallucinations (10-19%)
- ◆ Somnolence, sedation, “sleep attacks” (10-35%)
- ◆ Orthostatic hypotension (5-48%)
- ◆ Problems with impulse control reported
- ◆ May cause LESS motor fluctuations but MORE psychosis than levodopa



Sinemet vs. Dopamine Agonist

- ◆ For the older, or more severe patient, begin with carbidopa/levodopa and add a dopamine agonist if needed.
- ◆ For the younger, or less affected patient, start with a dopamine agonist and add carbidopa/levodopa when and if it is needed.



Marcia: Part V

- ◆ A couple of years after her retirement, symptoms again break through, and supplementary ropinirole (Requip) is again effective for about a year. When her symptoms break through further, she is referred to a neurologist, who uses entacapone (Comtan) to extend the effectiveness of levodopa.



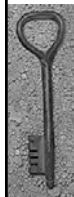
Catechol-O-methyltransferase (COMT) Inhibitors

- ◆ Inhibition of peripheral levodopa metabolism
- ◆ NOT FOR MONOTHERAPY
- ◆ Little or no change in C_{max} or T_{max} with repeated doses
- ◆ Levodopa dose should be reduced 30% when initiating
- ◆ Place in therapy: strong evidence for reducing “off” time



Catechol-O-methyltransferase (COMT) Inhibitors

- ◆ Tolcapone (Tasmar): not widely used due to hepatotoxicity
- ◆ Entacapone (Comtan)
 - 200 mg with each dose of levodopa/carbidopa, up to 8 times daily



COMT Inhibitors: Adverse Effects

- ◆ Brownish/orange discoloration of urine
- ◆ Increase in dopaminergic events (nausea*, postural hypotension, dyskinesias*, hallucinations)
- ◆ Mild to moderate gastrointestinal events (delayed-onset diarrhea at 6 to 8 weeks)

* most frequently reported adverse dopaminergic events



Carbidopa/Levodopa/Entacapone (Stalevo)

- ◆ New combination formulation
- ◆ Three strengths
 - Stalevo 50: 12.5 mg carbidopa, 50 mg levodopa, 200 mg entacapone
 - Stalevo 100: 25mg/100 mg/200 mg
 - Stalevo 150: 37.5 mg/150 mg/200 mg
 - Stalevo 200: 50 mg/200 mg/200 mg



Deep Brain Stimulation (DBS)

- ◆ Much like a cardiac pacemaker, a subcutaneous pulse generator is placed in the chest area and is connected to an electrode in the thalamus
- ◆ Can adjust DBS as needed
- ◆ Can improve tremor in seconds after placement (40%-75% decrease)
- ◆ Bradykinesia and rigidity may remain



Pharmacist's Role in Parkinson's

- ◆ Recording medication administrations times as well as duration of "on" and "off" times
- ◆ Maintain a detailed medication history; patients often adjust their own medications
- ◆ Adjust medications to lifestyle
- ◆ Counsel on potential drug interactions with OTCs
- ◆ Monitor for common side effects
- ◆ Screen for depression



Web Resources for Parkinson's

- ◆ American Parkinson's Disease Association
 - www.apdaparkinson.org
- ◆ APDA Iowa Chapter
 - www.apdaiowa.org
- ◆ Parkinson's Disease Foundation
 - www.pdf.org
- ◆ National Parkinson Foundation
 - www.parkinson.org



Web Resources for Parkinson's

- ◆ Michael J. Fox Foundation
 - www.michaeljfox.org
- ◆ Parkinson's Action Network
 - www.parkinsonsaction.org
- ◆ Parkinson Alliance
 - www.parkinsonalliance.org
- ◆ Parkinson's Institute
 - www.thepi.org