Disclosure

- I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this presentation.
- This discussion will include the use of medications for off-label indications.
Objectives

- Identify features of Parkinson’s Disease
- Evaluate medications and their use in treating Parkinsonian features
- Select patient assessment parameters to guide effective medication use

Parkinson’s Disease
Pathophysiology

- Characterized by dopamine deficiency
  - Loss of dopaminergic neurons in substantia nigra
    - Risk factors
      - Age - 60 yrs average age at onset
      - Gender - men more frequently than women
      - Environmental toxins
      - Drug induced symptoms

Parkinson’s and Parkinson’s-Plus Syndromes

- Idiopathic Parkinson’s Disease (IPD)
  - Most common presentation
    - Approximately 1% of population over 60 yrs

- Drug induced

- Multiple System Atrophy (MSA)
  - 3 per 100,000 older than 50 yrs
  - Parkinsonian feature and/or autonomic dysfunction
  - Most progress to developing Parkinsonian features
  - Not very responsive to levodopa
Parkinson’s-Plus Syndromes

- Progressive Supranuclear Palsy (PSP)
  - 5 per 100,000 older than 50 yrs
  - Less tremor than IPD
  - More falls early in disease
  - Levodopa not very helpful

- Corticobasal Degeneration
  - 1-2 per 100,000
  - Cognitive dysfunction
  - Myoclonus/dystonia

- Vascular Parkinsonism
  - Develops from multiple strokes

Drug Induced Parkinsonism

- Medications with highest risk
  - Anti-psychotics
    - Typical and atypical
  - Anti-emetics
    - Phenothiazines, metoclopramide
  - Neurotransmitter depletors
    - Reserpine, methylidopa
Disease Presentation/Diagnosis

- Clinical diagnosis
- Four cardinal features
  - Bradykinesia
  - Rigidity
  - Tremor
  - Postural instability
- Life expectancy 15-20yrs from time of diagnosis

Motor Symptoms/Features of Parkinson’s

- Cogwheel rigidity  
- Micrographia
- Decreased facial expression
- Dysphagia
- Shuffling gait  
- Decreased arm swing
- Decreased dexterity
- Start hesitancy with freezing episodes  
- Dystonia  
- Soft speech

** may contribute to falls
Non-Motor Features of Parkinson’s

- Autonomic dysfunction
  - Orthostatic hypotension **
  - Impaired intestinal motility/constipation
  - Urinary disturbances
  - Sexual dysfunction
  - Sweating
- Anxiety
- Depression
- Sialorrhea
- Dementia
- Hallucinations

** may contribute to falls

Disease Progression

- Early symptoms of tremor, bradykinesia, rigidity typically seen first
  - May present unilaterally and become bilateral with progression of disease
- Postural instability
  - Seen in more advanced disease

- Common cause of death
  - Pulmonary infection/aspiration
  - Urinary tract infection/sepsis
  - DVT/PE complications
  - Complications secondary to falls and fractures
Case Presentation: Mrs. M.

- Mrs. M is an 88 yo female with primary diagnosis of Parkinson’s. She lives at home with family as caregivers. She is still ambulatory with assistance and able to remain continent of bowel/bladder as long as she can get to commode.
- Current complaint: Leg pain and movements at night. Right leg shakes more than left. She is unaware of shaking, but it wakes husband.
- Current Meds:
  - Carbidopa/Levodopa CR (Sinemet CR®) 50/200 2 tablets q8h
  - Aspirin 81mg qd
  - Furosemide (Lasix®) 20mg qam
  - Digoxin (Lanoxin®) 0.25mg qd
  - Donepezil (Aricept®) 5mg qd
  - Naproxen (Aleve®) 220mg q12h prn

Medication Treatment

- What’s the Goal?
  - Early stage vs End stage
  - Symptom management
  - Functional status
  - Minimizing adverse reactions
  - Reduce polypharmacy
Medication Options

- Dopaminergic agents
  - Carbidopa/levodopa
  - Dopamine agonists
- COMT inhibitors
- Amantadine
- Anticholinergics
- MAO-B inhibitors

Parkinson’s Disease

- Dopamine
- Dopamine Agonist
- Levodopa
- Monoamine oxidase-B
- Blood Brain Barrier
- 3 O-methyltyrosine
- Decarboxylase inhibitor
- Cathecol-O-methyltransferase inhibitor
Dopaminergic Agents

- **Carbidopa/levodopa**
  - Levodopa is what the brain needs
  - Carbidopa inhibits decarboxylation of levodopa in the peripheral circulation
  - Carbidopa has no activity itself
  - Carbidopa can minimize peripheral side effects of Levodopa such as nausea/vomiting
  - Most effective medication for treating Parkinson’s Disease
  - Side effects
    - Nausea
    - Postural hypotension
    - Hallucinations
    - Dyskinesias
  - Administration on empty stomach
    - Protein and iron decrease absorption

### Carbidopa/Levodopa Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strengths</th>
<th>Onset</th>
<th>Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR Tablet (Sinemet®)</td>
<td>10/100, 25/100, 25/250</td>
<td>15-30 min</td>
<td>2-4 hours</td>
<td>$0.80-$1.00 per tablet</td>
</tr>
<tr>
<td>ODT Tablet (Parcopa®)</td>
<td>10/100, 25/100, 25/250</td>
<td>15-30 min</td>
<td>2-4 hours</td>
<td>$1.20-$1.75 per tablet</td>
</tr>
<tr>
<td>ER Tablet (Sinemet CR®)</td>
<td>25/100, 50/200</td>
<td>30-60 min</td>
<td>4-6 hours</td>
<td>$1.00-$1.80 per tablet</td>
</tr>
<tr>
<td>IR/ER Capsule (Rytary®)</td>
<td>23.75/95, 36.25/145, 48.75/195, 61.25/245</td>
<td>15-30min</td>
<td>4-6 hours</td>
<td>$2.75-$3.50 per capsule</td>
</tr>
<tr>
<td>Enteral Suspension (Duopa®)</td>
<td>4.63/20/ml, Peak 2.5hr</td>
<td>30-60min, 16 hr infusion</td>
<td>Via J-tube</td>
<td>$242 per day</td>
</tr>
</tbody>
</table>
Take Note!

Levodopa is the most effective treatment for Parkinson’s symptoms, but benefit will decrease as disease progresses.

Side effects may outweigh benefit in advanced disease.

Parkinson’s Disease

Dopamine

Dopamine

Agonist

Levodopa

Decarboxylase inhibitor

Blood Brain Barrier

3 O-methyldopa

Entacapone
COMT-Inhibitors

- Entacapone (Comtan®)
- Tolcapone (Tasmar®)
- Entacapone/carbidopa/levodopa (Stalevo®)

- Inhibitor of catechol-O-methyltransferase (COMT)
- Allows levodopa serum levels to be increased
  - More levodopa around to cross blood brain barrier = more dopamine
- MUST be given with carbidopa/levodopa
- Tolcapone associated with severe hepatotoxicity
- Helpful for end of dose failures

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COMT-Inhibitors

- Entacapone 200mg with each dose of Carb/Levo
  - Cost $3.95 per tab
- Tolcapone 100mg three times daily
  - Cost $117 per tab!
- Carbidopa/Levodopa/Entacapone
  - All have 200mg Entacapone per tab
  - Various strengths of Carb/Levo from 12.5/50 up to 50/200
  - Cost $3.75 per tab, all strengths
  - Manufacturer recommends not crushing tablet
Dopamine Agonists

- Mimics natural dopamine effects
- Can be used as mono or combo therapy
- Useful for on/off periods and end of dose failure
- Side effects
  - Nausea/vomiting
  - Dizziness
  - Sedation
  - Postural hypotension
  - Confusion
  - Hallucination
  - Abnormal dreams
  - Dry mouth
- Frequently used for RLS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strengths</th>
<th>Dosing</th>
<th>Approx Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole IR Tablets</td>
<td>0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg, 5mg</td>
<td>Initial three times daily, titrated to effect</td>
<td>$2.50 per tab</td>
</tr>
<tr>
<td>Ropinirole ER Tablets</td>
<td>2mg, 4mg, 6mg, 8mg, 12mg</td>
<td>Once daily</td>
<td>$2.70-$13.70 each dose dependent</td>
</tr>
<tr>
<td>Pramipexole IR tablets</td>
<td>0.125mg, 0.25mg, 0.5mg, 0.75mg, 1mg, 1.5mg</td>
<td>Initial three times daily, titrated to effect</td>
<td>$3 per tab</td>
</tr>
<tr>
<td>Pramipexole ER tablets</td>
<td>0.375mg, 0.75mg, 1.5mg, 2.25mg, 3mg, 4.5mg</td>
<td>Once daily</td>
<td>$16 per tab</td>
</tr>
<tr>
<td>Rotigotine patches</td>
<td>1mg, 2mg, 3mg, 4mg, 6mg, 8mg</td>
<td>Once daily</td>
<td>$23 per patch</td>
</tr>
<tr>
<td>Apomorphine (Apokyn®)</td>
<td>10mg/ml inj 3ml cartridge for injector pen</td>
<td>2mg SC and titrate to max 6mg per dose TID</td>
<td>$80 per 2mg dose</td>
</tr>
</tbody>
</table>
Dopamine Agonist

- Apomorphine (Apokyn®)
  - Very potent
  - Requires medical supervision for first test dose
  - Side effects:
    - Nausea, vomiting, drowsiness, dizziness, orthostatic hypotension, dyskinesia, falls, chest pain/pressure, hallucinations, confusion,
  - Antiemetic to begin prior to administration
    - Don’t use dopamine antagonist or 5-HT3 antagonists
    - Trimethobenzamide 300mg caps or 200mg/2ml IM only
  - Available only from specialty pharmacies
  - SC injection with injector pen device

Antiviral

- Amantadine (Symmetrel®)
  - Blocks reuptake of dopamine into presynaptic neurons and increases dopamine release from presynaptic fibers
  - NMDA weak antagonist
  - Used early in diagnosis for tremors
  - May be used for bradykinesias, rigidity,
  - Adjunct in later disease for dyskinesias caused by levodopa
  - Side effects similar to anticholinergics
  - Dosed 100mg twice daily
    - Capsules, tablets 100mg
      - Cost $2 each
    - Syrup 50mg/5ml
      - Cost $1.50 per 100mg dose
Anticholinergics

- Most useful for tremors and rigidity
- Treatment in early disease
- Side effects: SLUDGE

Trihexyphenidyl (Artane®)
- Starting doses 1mg QD and may titrate up every 3-5 days
- Range 3-6mg/day in divided doses with levodopa
- May use higher doses 6-10mg/day in divided doses as monotherapy
- Tabs 2mg, 5mg and liq 0.4mg/ml
  - 2mg=$0.20, 5mg=$0.35, Liq 2mg dose =$0.32

Benztropine (Cogentin®)
- Starting doses 0.5mg-1mg QHS and may titrate every 5 days
- Range 1-2mg QD, up to max 6mg/day
- Tabs 0.5mg, 1mg, 2mg and inj 1mg/ml
  - 0.5mg=$0.38, 1mg=$0.40, 2mg= $0.52, and inj 2mg/2ml $59

Parkinson’s Disease

Dopamine

Levodopa

Monoamine oxidase-B

Cathecol-O-methyltransferase inhibitor

Selegiline, Rasagiline

Blood Brain Barrier

Decarboxylase inhibitor

3 O-methylidopa
MAO-B Inhibitors

- Increases dopamine levels by inhibiting reuptake at synapse
- Monotherapy early in disease
- Adjunct with levodopa in later disease
- Side effects: dizziness, insomnia, hallucinations, nightmares, nausea, orthostatic hypotension
- Drug/food interactions:
  - Serotonergic meds, meperidine, SSRI, TCAs, SNRI, etc.
  - Tyramine containing foods/drinks – ok at normal doses with low tyramine containing foods. Concern with high content foods may cause hypertensive crisis
- Possible neuroprotective effect?
  - ADAGIO study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Strengths</th>
<th>Dosing</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selegiline (Eldepryl®)</td>
<td>Tablet, Capsule</td>
<td>5mg</td>
<td>5mg BID</td>
<td>$2.30 per dose</td>
</tr>
<tr>
<td>Selegiline ODT (Zelapar®)</td>
<td>Tablet</td>
<td>1.25mg</td>
<td>1.25mg QD</td>
<td>$81 per dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max 2.5mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selegiline (Emsam®)</td>
<td>Patch</td>
<td>6mg, 9mg, 12mg</td>
<td>1 patch q24h</td>
<td>$60 per patch</td>
</tr>
<tr>
<td>Rasagiline (Azilect®)</td>
<td>Tablet</td>
<td>0.5mg, 1mg</td>
<td>0.5mg·1mg QD</td>
<td>$23 per dose</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
Take Note!

Medications are available in many different dosage forms.

Just because it’s available, doesn’t mean we need to use it!

Will a change in dosage form really fix the problem?
  ➢ Dysphagia from disease progression?
  ➢ Cognitive impairment?
Back to Mrs. M

- Leg pain and movements at night
  - Family called it RLS
  - Ropinirole (Requip®) 0.25mg qhs started
  - Other causes of movement or pain?

- Ropinirole was titrated up to 1.5mg QHS over the next month
  - She is still waking in the night with pain
  - She wants to get up and stand, but is a fall risk

- New confusion and hallucinations
  - Family wondered if it was related to Ropinirole

Case: Mrs. M

- Ropinirole (Requip®) stopped
- Quetiapine (Seroquel®) 25mg qhs started for agitation and hallucinations
  - Family gives at 9:30pm and pt sleeping until 11am
  - Family very happy with sleep
  - Now she isn’t able to take her morning Carb/Levo CR (Sinemet CR®)
    - Having trouble swallowing tabs whole

- Patient assessment: What is goal of therapy at this time?
  - Minimally ambulatory
  - Needs assistance with ADLs
  - Continent of bladder/bowel if helped to commode
    - Difficult to do when she doesn’t take Carb/Levo CR in morning
  - Family reports agitation, hallucinations, paranoia
Case: Mrs. M. 1 month later

- Carb/Levo CR 50/200 AM dose changed to Carb/Levo IR 25/100
  - Patient has been chewing tablets now
- Patient assessment – Review of goals
  - Stand/pivot with max assist
  - No independent ADLs
  - Incontinent of bladder and bowel
- Daughter asked to change to Carb/Levo IR 25/100 three tabs QID
  - Dosing frequency makes sense
  - But what is the Carb/Levo treating at this time?
    - What function is the Carb/Levo preserving?

Motor Fluctuations

- “Off” period
  - Response to medication wears off and symptoms return
  - Off periods increase as disease progresses
  - Also called “end-of-dose deterioration” or “wearing off” phenomenon
  - Dystonic muscle cramping can occur
- “On” period
  - Time when patient responds well to medications
  - Decreases as disease progresses
- Diphasic dyskinesia
  - Alternate pattern of dystonia/dyskinesia-improvement-dystonia/dyskinesia
  - D-I-D
  - Associated with beginning and end of dose
Motor Fluctuations

- **Dyskinesia**
  - Involuntary, choreiform movements, dystonia, tic, myoclonus,
  - Related to dopaminergic medication
  - Risk of injury
  - Social embarrassment/isolation

- **Freezing**
  - Transient, lasts several seconds
  - Glued to the ground
  - Caused by low dopamine levels in CNS

The Balancing Act

- Managing symptoms of disease vs medication complications
  - Motor fluctuation associated with levodopa therapy
  - Wearing off/end of dose
    - Adjust dosing interval
  - Off dyskinesia
    - Low dopamine level, may be seen in early morning as dystonia
    - CR formulations, COMT inhibitor,
  - Peak dose dyskinesia
    - Adjust dose of levodopa
    - Add Dopamine agonist
  - Dose failure
    - Food related/GI related?
Discontinuing Therapy

➢ When should therapy be stopped?
  ● When side effects become severe
  ● When functional status is limited by disease progression

➢ How should therapy be stopped?
  ● Most medications should be tapered
  ● Abrupt discontinuation of dopaminergic medications can precipitate neuroleptic malignant syndrome (NMS)

Discontinuing Therapy

➢ Which medications should be the first to go?
  ● Anticholinergics
    ▪ In general, avoid use in elderly due to cognitive effects
  ● Amantadine
    ▪ Anticholinergic side effects can be problematic in elderly patients
    ▪ Taper slowly to avoid NMS
  ● MAO-B Inhibitors
    ▪ Can exacerbate dyskinesias from carb/levo
    ▪ Must be tapered, consider 10% reduction per week
Discontinuing Medications

- **Dopamine agonists**
  - When neuropsychiatric symptoms present
  - Taper over 1-2 weeks, do not stop abruptly

- **COMT- Inhibitors**
  - When dyskinesias, motor fluctuations outweigh benefit
  - Taper to avoid NMS

- **Carb/Levo**
  - For peak dose dyskinesias decrease dose every 3-4 days until improvement
  - To discontinue, reduce dose every 3-4 days until stopped.

Symptom Management

- **Dopamine blocking medications treat:**
  - Psychosis symptoms
  - Nausea/vomiting
  - Hiccups
  - GI motility issues
Antidopaminergic medications

- Butyrophenones
  - Haloperidol (Haldol®)
    - Blocks D₂ receptors in the brain
- Phenothiazines
  - Chlorpromazine (Thorazine®), Perphenazine (Trilafon®), Prochlorperazine (Compazine®), Promethazine (Phenergan®)
    - All block dopamine
    - Prochlorperazine and Promethazine have anticholinergic and antihistamine effect
- Can worsen Parkinsonian symptoms
  - Always a contraindication in Parkinson's EOL care?

Antidopamine Medications

- Atypical antipsychotics
  - Clozapine (Clozaril®)
  - Quetiapine (Seroquel®)
  - Risperidone (Risperdal®)
  - Olanzapine (Zyprexa®)
  - Aripiprazole (Abilify®)
  - Ziprasidone (Geodon®)
  - Lurasidone (Latuda®)
  - Brexpiprazole (Rexulti®)
- Most still have potential to worsen Parkinson's symptoms
- Clozapine has little to no impact on Parkinson’s symptoms, but use can be cumbersome
  - Restrictive access
  - Labs are needed
    - Hospice patients not excluded
Antidopamine Medications

- Metoclopramide
  - Blocks dopamine and serotonin receptors in chemoreceptor trigger zone
  - Increases GI motility
  - Can worsen Parkinsonian symptoms, cause extra-pyramidal symptoms

- Alternatives?
  - Erythromycin for GI motility?
  - Domperidone
    - Not available as commercially available product
    - Use restricted through expanded access investigational new drug application (IND)

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Take Note!

Anti-dopamine medications have a general contraindication in Parkinson’s Disease.

But their use may be appropriate if benefit outweighs risk, such as when use may not be expected to significantly impact functional status.
**Miscellaneous Medications**

- **Anticholinesterase inhibitors**
  - For dementia symptoms
    - Donepezil (Aricept®), Galantamine (Razadyne®) are off label
    - Rivastigmine (Exelon®) has approved use
  - Gait disturbances?
    - ReSpond trial
      - Rivastigmine (Exelon®) studied gait, balance, falls
      - Small sample, but benefit seen
      - Useful in end of life care?

- **Antidepressants**
  - Caution with use of MAO-B inhibitors – 2 week wash out period

- **Anxiolytics**
  - Benzodiazepines may paradoxically worsen delirium symptoms

**Key Points**

- Parkinson’s disease is a progressive neurodegenerative disease
  - Medications will not stop or reverse disease process
- Medication therapy is aimed at replacing lost dopamine
  - Side effects of dopaminergic agents will limit use in ES disease
- Patient assessment and evaluation of goals is paramount
  - Patient functional status should guide therapy
- Less is More in end of life care
  - Consider reducing medications when side effect burden is great
  - Reduce polypharmacy
Questions?

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HospiScript Services
Imiles@hospiscript.com

References

References


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