Parkinson’s Disease: the ABC’s of PD Drug Therapy

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Adjunct Faculty University at Buffalo SoPPS
Disclosure

• No financial interests or relationships to disclose
Objectives

• Design a patient specific drug regimen for a patient diagnosed with Parkinson’s Disease (PD)

• Identify medications that can cause drug-induced Parkinsonism and medications that can exacerbate PD

• Evaluate signs/symptoms of PD psychosis and recommend therapy modification, including antipsychotic treatment, to increase patient quality of life
Epidemiology

• Approx. 1% population >60 years old
  • 3.5% 85-89 years

• 60,000 new cases per year

• Estimates 1 million in United States / 5 million worldwide

• Prognosis:
  • Decreased life expectancy
  • Current medical treatments do not alter mortality
Cause

• Genetic factors (10% of cases)
  • LRRK2 mutation
  • Glucocerebrosidase gene mutation
  • Parkin mutation

• Environmental factors
  • Industrial exposure
  • Heavy metals (manganese, lead, copper)
  • Pesticides
Pathophysiology

Chronic, progressive, neurodegenerative disorder

- Progressive premature death of dopaminergic neurons
  - Motor symptoms: 30-70% neuron loss in substantia nigra
  - Cognitive dysfunction/mood disorders/impuls control: outside of the basal ganglia or in serotonergic and noradrenergic systems
  - Autonomic syndromes: outside of brain – spinal cord, peripheral autonomic nervous system
Pathophysiology

Neurodegenerative disease:
- Abnormal protein aggregates in midbrain, brain stem, and olfactory bulb
  - Lewy Bodies
  - α-synuclein
Pathophysiology

- Braak staging of Lewy Body deposition:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites Affected</th>
<th>Major Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Dorsal motor nucleus of vagus nerve and olfactory tract</td>
<td>Constipation, Loss of smell</td>
</tr>
<tr>
<td>II</td>
<td>Locus coeruleus &amp; subcoeruleus complex</td>
<td>Sleep disorder, Mood dysfunction</td>
</tr>
<tr>
<td>III</td>
<td>Substantia nigra</td>
<td>Motor symptoms</td>
</tr>
<tr>
<td>IV-VI</td>
<td>Cortical involvement</td>
<td>Dementia, Psychosis</td>
</tr>
</tbody>
</table>

Diagnosis

- Neuroimaging:
  - DaTscan
  - MRI
  - Transcranial Doppler ultrasonography
  - PET
  - SPECT

- Biomarkers
  - $\alpha$-synuclein in CSF

Diagnosis

• Clinical features and history of symptoms:
  • Asymmetric motor manifestations
  • Resting tremor
  • Hypophonia
  • Masked facial expression
  • Micrographia
  • Stiffness/rigidity
  • Bradykinesia
  • Shuffling gait
  • Poor balance

Diagnosis

• Neurologic exam:
  • Limb stiffness?
  • Animated expression?
  • Tremor?
  • Normal gait? Arm swing present?
  • Balance?
  • Ease of rising from sitting?
<table>
<thead>
<tr>
<th></th>
<th>Depression / anxiety</th>
<th>Hallucinations, psychosis, delusions</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cognitive impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Compulsions/impulsivity</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td>Constipation</td>
<td>Urinary urgency/incontinence</td>
<td>Orthostasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>Sleep</td>
<td>Restless leg syndrome (RLS)</td>
<td>Insomnia</td>
<td>Daytime somnolence</td>
</tr>
<tr>
<td>Sensory</td>
<td>Pain</td>
<td>Numbness</td>
<td>Parathesias</td>
</tr>
<tr>
<td>Other</td>
<td>Olfactory impairment / odor identification deficit</td>
<td>Dysarthria</td>
<td>Hypophonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diplopia</td>
</tr>
</tbody>
</table>

# Early v. Late Symptoms

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor</strong></td>
<td><strong>Motor fluctuations</strong>&lt;br&gt;Choreiform dyskinesias&lt;br&gt;Gait freezing&lt;br&gt;Falls</td>
</tr>
<tr>
<td>Tremor of hand, jaw, or foot&lt;br&gt;Bradykinesia&lt;br&gt;Decreased facial expression&lt;br&gt;Decreased arm swing or leg dragging&lt;br&gt;Frozen shoulder&lt;br&gt;Stiffness/numbness/pain in limb&lt;br&gt;Difficulty turning in bed&lt;br&gt;Micrographia&lt;br&gt;Soft Voice</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Motor</strong></td>
<td><strong>Dysphagia</strong>&lt;br&gt;Neuropsychiatric symptoms&lt;br&gt;Dementia&lt;br&gt;Autonomic disturbances&lt;br&gt;Seborrheic dermatitis</td>
</tr>
<tr>
<td>Constipation (approx. 30%)&lt;br&gt;REM sleep behavior disorder&lt;br&gt;Depression&lt;br&gt;Olfactory impairment (up to 97%)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment

• Goals:
  • Increase dopamine (DA) in the striatum

• Challenges:
  • Slow progression (targeting in clinical trials)
  • Symptom relief v. modifying disease progression
  • Multiple medication adjustments and adjunctive treatments required
## Available Treatment Options

<table>
<thead>
<tr>
<th>DA precursors</th>
<th>Levodopa (L-dopa)</th>
<th>Immediate precursor of DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA agonists</td>
<td>Apomorphine</td>
<td>Stimulate DA receptors in the brain</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ropinirole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pramipexole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rotigotine</td>
<td></td>
</tr>
<tr>
<td>MAO-B inhibitors</td>
<td>Selegiline</td>
<td>Inhibits MAO-B which degrades DA</td>
</tr>
<tr>
<td></td>
<td>Rasagiline</td>
<td></td>
</tr>
<tr>
<td>COMT inhibitors</td>
<td>Entacapone</td>
<td>Reduces peripheral conversion of L-dopa</td>
</tr>
<tr>
<td></td>
<td>Tolcapone</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Benztropine</td>
<td>Reduces cholinergic activity (caused by loss of DA) and reduces tremor</td>
</tr>
<tr>
<td></td>
<td>Trihexyphenidyl</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Algorithm

- Levodopa monotherapy
- MAO-B Inhibitors
- Dopamine Agonists
Adjunctive Treatment

- **MAO-B Inhibitors**
  - +/- benefit in “off” time
  - More effective in earlier “wearing off” v. later “on and off”

- **Dopamine Agonists**
  - More off time reduction
  - Non-ergot derived*

- **COMT inhibitors**
  - Lower risk hallucinations
  - Fewer ADE

- **Anticholinergics** → increased risk cognitive impairment, hallucinations, falls, urinary retention

- **Apomorphine** +/- efficacy, not first line in adjunct

- **Amantadine** → effective for L-dopa dyskinesias

Early Onset PD

• Early onset (Young-Onset PD):
  • <50 years old
  • Slower disease progression
  • More likely to have levodopa induced dyskinesias
    • DA agonist, MOA-B inhibitors, anticholinergics first line treatment
Levodopa

- Precursor to dopamine
- Combination products:
  - Carbidopa/Levodopa (also available: ODT, controlled release, extended release, enteral suspension)
  - Carbidopa/Levodopa/Entacapone
- Maintenance dose:
  - 300-1600 mg/day (L-dopa)
Levodopa

• “Off” and “On” phenomena
  • Short $t_{1/2}$
  • Loss of neuronal storage capability
• “On”/Peak-dose dyskinesias
  • Choreiform movements
  • Peak striatal dopamine levels
  • Elevated glutamate levels
• “Wearing off”
  • As PD progresses, duration of action significantly decreases
<table>
<thead>
<tr>
<th>Effect</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| End of dose “wearing off”     | Increase frequency of L-dopa  
Add either:  
COMT inhibitor  
MAO-B inhibitor  
DA agonist |
| Delayed “on” (or no on response) | L-dopa on empty stomach  
L-dopa ODT  
Switch to IR L-dopa (if taking CR)  
Apomorphine SQ |
| Freezing/start hesitation     | Increase L-dopa  
Add either:  
MAO-B inhibitor  
DA agonist  
Physical therapy |
| Peak dose dyskinesia          | Decrease L-dopa doses  
Add amantadine |
Dopamine Agonists

• Stimulate DA receptors in the brain
• Not as potent as carbidopa/levodopa
  • Less likely to cause dyskinesias
• Monotherapy or combination therapy
  • Apomorphine 3-12 mg/day (injection)
  • Bromocriptine 15-40 mg/day
  • Pramipexole (ER) 1.5-4.5 mg/day
  • Ropinirole (XL) 8-24 mg/day
  • Rotigotine 2-8 mg/day
MAO-B Inhibitors

• Block MAO-B enzyme that breaks down levodopa
• Delay need for carbidopa/levodopa if prescribed in early PD
• Maintenance doses:
  • Rasagiline 0.5-1 mg/day
  • Selegiline 5-10 mg/day
  • Selegiline ODT 1.25-2.5 mg/day
COMT Inhibitors

- No effects on PD if used as monotherapy
- Prolongs effect of levodopa
- Maintenance doses:
  - Entacapone 200-1600 mg/day
  - Tolcapone 300-600 mg/day
Other Medications

• Anticholinergics
  • Benztropine 1-6 mg/day
  • Trihexyphenidyl 6015 mg/day

• Amantadine
  • Tremor in early PD
  • Reduce dyskinesias in DA medication
  • 200-300 mg/day
Non-motor Symptoms

• Concomitant emotional, cognitive, and behavioral features cause significant disability

• Research shifting towards non-motor symptoms of PD:
  • Depression
  • Anxiety
  • Apathy
  • Dementia
  • Psychosis
Psychosis

• 20-40% of PD patients
• Hallucinations, delusions, illusions
• PD psychosis v. Schizophrenia / Schizoaffective disorder
  • Psychosis develops after PD diagnosis
  • Primarily paranoid delusions
  • Visual hallucinations/sensory disturbances (presence hallucinations)
    • Evening time
  • Worsens over time
Psychosis

• PD drugs increase susceptibility to psychosis
  • Hyperensitization of DA receptors in niagrostriatal pathway due to chronic stimulation
  • Misattributions of internal stimuli
  • Dysfunction of limbic structures

• Disease progression and changes in neurochemical processes and structural pathophysiology
Psychosis

Brainstem & Sleep Dysfunction

Visual Dysfunction

Deep Brain Stimulation Surgery

Parkinson’s Disease Medications

Cortical Pathology

Genetics, Neurochemical Abnormalities

Psychosis

• Treatment:
  • Evaluate for underlying condition
  • Reduction of anti-PD drugs
  • Reduce/remove medications that can induce/exacerbate psychosis

Psychosis

• Medications that can induce/worsen psychosis:
  • Tricyclic antidepressants
  • Antihistamines
  • Anticholinergics
  • Amantadine
  • DA agonists
  • COMT inhibitors
  • L-dopa
Psychosis

• Treatment:
  • Evaluate for underlying condition
  • Reduction of anti-PD drugs
  • Reduce/remove medications that can induce parkinsonism
  • Switch levodopa from ER to immediate release
  • Add antipsychotic medication
    • BBW: increased risk of mortality in elderly patients with dementia
    • Second generation antipsychotics
      • Metabolic syndrome
      • Orthostatic hypotension

Clozapine

• Safety, tolerability, efficacy shown in multiple RCT and open label trials
• Psychosis treatment reached in doses as small as 6.25 mg/day
• Minimal effects on tremor/movement symptoms of PD
• Patients must be enrolled in the REMS program
  • Agranulocytosis
• Worsened PD symptoms in doses >150 mg/day
Quetiapine

• 12.5-25 mg at bedtime
  • Studies show tolerability up to 200 mg
• Positive effect on sleep architecture
• Minimal effect on worsening motor symptoms

Psychosis Treatment Misc.

• Risperidone
  • Majority open label studies
  • Mixed results in efficacy
  • Reports of severely worsening motor symptoms

• Ziprasidone
  • Lacks data in regards to proven efficacy
  • Risk of QTc prolongation

• Aripiprazole
  • Studies with small n
  • Significant akathisia reported

Pimavanserin

• First FDA approved medication for PD psychosis
• 5-HT2A receptor inverse agonist
  • No activity on DA receptors like other antipsychotic medications
  • Not found to worsen PD motor symptoms
• 17 – 34 mg daily

• Same safety concerns as antipsychotics:
  • Neuroleptic sensitivity reactions, increased risk of mortality, stroke, and pulmonary embolism, and accelerated cognitive decline
  • Awaiting further post marketing information and longer duration of use

Dementia

• Donepezil
  • Predominately open label studies
  • Modest efficacy in symptoms of dementia and psychosis
    • Lack of statistical significance in trials

• Galantamine
  • Additional MOA of acting on nicotinic receptors
    • Increases release of dopamine
  • Small studies
  • Improvement in dementia symptoms and QOL
    • Worsening of tremor frequently reported

Litvienko IV et al. Neurosci Behav Physiol. 2008 Nov;38(9):937-945
Dementia

• Rivastigmine – approved for PD dementia
  • Dual action: acetylcholinesterase and butyrylcholinesterase inhibitor
  • Improves: cognition, attention and executive functions, ADLs, and behavioral symptoms
  • 3-12 mg/day

Depression

• Underdiagnosed – approx. 50% diagnosed with PD meet criteria for major depressive disorder

• Mixed results with antidepressant therapy:
  • TCA’s
    • Improvement in sleep
  • Paroxetine & Venlafaxine
    • Improvements shown as early as 4 weeks
    • Significant improvements and responsiveness on depression and PD rating scales
Conclusion

• Pharmacotherapy initiation and selection is patient specific
  • Consider factors such as Young-Onset PD, most troublesome PD symptom, etc.

• Monitor patient for difficulties with non-motor symptoms as well as motor symptoms
  • Treatment of psychosis, dementia, and depression improves patient and care giver quality of life

• Target pharmacotherapy to address patient’s most bothersome symptoms
Questions?

Parkinson’s Disease: the ABC’s of PD Drug Therapy

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>MOA</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orotidine (ACR325) / Seridopidine (ACR343)</td>
<td>Saniona AB</td>
<td>D$_2$ modulators/stabilizers</td>
<td>Phase 2</td>
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<tr>
<td>AE04621 / AC04621</td>
<td>Lundbeck</td>
<td>D$_1$/D$_2$ agonist</td>
<td>Phase 1</td>
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<tr>
<td>PF-06649751</td>
<td>Pfizer</td>
<td>D$_1$ agonist</td>
<td>Phase 2</td>
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<tr>
<td>IRL-790</td>
<td>Integrated Research Laboratories</td>
<td>D$_2$ agonist</td>
<td>Phase 1b</td>
</tr>
<tr>
<td>LY3154207</td>
<td>Eli Lilly</td>
<td>D$_1$ potentiator</td>
<td>Phase 1</td>
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<tr>
<td>CLR4001</td>
<td>Clera Inc.</td>
<td>D$_2$ agonist</td>
<td>Phase 2a</td>
</tr>
<tr>
<td>SLS-006</td>
<td>Seelos Therapeutics/Pfizer</td>
<td>D$_2$/D$_3$ partial agonist</td>
<td>Phase 3</td>
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<tr>
<td>RP-5063 / RP-5000</td>
<td>Reviva Pharmaceuticals</td>
<td>D$<em>2$/D$<em>3$/5HT$</em>{1A}$/5HT$</em>{2A}$ partial agonist, 5HT$_6$/5HT$_7$ antagonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>KDT3594</td>
<td>Kissei Pharmaceuticals</td>
<td>D$_2$ agonist</td>
<td>Phase 1</td>
</tr>
<tr>
<td>YKP-10461</td>
<td>SK Biopharmaceuticals/Celerion</td>
<td>Reversible MAO-B inhibitor</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ODM-104 (in combo with l-DOPA)</td>
<td>Orion Pharma</td>
<td>COMT inhibitor</td>
<td>Phase 2</td>
</tr>
<tr>
<td>SAGE-217</td>
<td>Sage Therapeutics</td>
<td>GABA modulation</td>
<td>Phase 2</td>
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<tr>
<td>ODM-106</td>
<td>Orion Pharm</td>
<td>GABAB receptor modulator</td>
<td>Phase 1</td>
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<td>KW-6356</td>
<td>Lundbeck/Kyowoa Hakko Kirin</td>
<td>adenosine$_{2A}$ antagonist</td>
<td>Phase 2</td>
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<tr>
<td>Tozadenant (sYN-115)</td>
<td>Roche/Biotie Therapies</td>
<td>adenosine$_{2A}$ antagonist</td>
<td>Phase 3</td>
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<tr>
<td>Eltoprazine</td>
<td>Roche/Biotie Therapies</td>
<td>5HT$<em>{1A}$/5HT$</em>{1B}$ agonist, 5HT$_{2C}$ antagonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Landipirdine (SYN-120)</td>
<td>Biotie Therapies</td>
<td>5HT$<em>6$/5HT$</em>{2A}$ antagonist</td>
<td>Phase 2</td>
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<tr>
<td>Foliglurax (PXT-002331)</td>
<td>Prexton Therapeutics</td>
<td>Glutamate modulator</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

Appendix A

UK Parkinson’s Disease Society Brain Bank for diagnosing Parkinson’s disease:

• Bradykinesia and at least one of the following:
  • Rigidity
  • Resting tremor
  • Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

• Exclusion of other causes of parkinsonism

• At least three of the following supportive (prospective) features:
  • Unilateral onset
  • Persistent asymmetry primarily affecting the side of onset
  • Resting tremor (hand, leg or jaw, asymmetric, disappears with action)
  • Excellent response to levodopa (70-100%)
  • Progressive disorder
  • Severe levodopa-induced chorea (dyskinesias)
  • Levodopa response for five years of more
  • Clinical course of 10 years or more

## Appendix B

### Differentiating between PD and Essential Tremor

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>Essential Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&gt;60 y/o</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Facial Expression</strong></td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Family History</strong></td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Gait</strong></td>
<td>Unstable</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Freezing</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle Tone</strong></td>
<td>Weakness, cogwheel rigidity</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Tremor Characteristic</strong></td>
<td>Resting (pill rolling)</td>
<td>Postural</td>
</tr>
<tr>
<td></td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
</tbody>
</table>