Motor Fluctuations

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Loss of Dopamine (DA) Containing Neurons in PD

Loss of DA neurons in Substantia Nigra responsible for motor symptoms

Dopamine: A Neurotransmitter

Neurotransmitter: A chemical which transmits a signal from one neuron to another.
What are Dopamine Neurons Doing?

- They are sending a “steady” signal.
- Goal of medications is to “fix” the signal by either:
  1. Replacing Dopamine
  2. Stimulating Dopamine receptors directly
Agents Used in the Treatment of Parkinson’s Disease

- **Levodopa Preparations**
  - Carbidopa/levodopa IR
  - Rytary
  - Duopa

- **Helper Medications**
  - Dopa decarboxylase inhibitors
    - Carbidopa
    - Benserazide
  - COMT inhibitors
    - Entacapone
    - Tolcapone
  - MAO-B inhibitors
    - Selegiline
    - Rasagiline
    - Safinamide

- **Dopamine Agonists**
  - Ropinirole
  - Pramipexole
  - Rotigotine
  - Apomorphine*

- **Anticholinergics**
  - Trihexyphenidyl
  - Benztropine

- **NMDA receptor antagonists**
  - Amantadine
  - Gocovri (Amantadine ER)
Carbidopa/Levodopa (Sinemet®)

- Levodopa is most powerful drug for PD
- Least side effects
- Generic, relatively cheap
- All patients respond
- Improves mortality rate

- Response changes over time due to changes in compensatory responses or further loss of nigrostriatal projections
- Chronic use of L-dopa does NOT enhance progression of pathology (Parkinnen et al 2011)
Absorption through gut to blood. L-dopa is an amino acid and is transported through “channels” along with other amino acids. Only a limited number of amino acids can be transported in a given time.
Getting L-dopa from Blood to Brain

**Blood-Brain Barrier:**
L-dopa will not simply diffuse into brain. It has to get through a barrier by being transported with other amino acids through channels.
It Takes Time to Get the L-dopa to the Brain

• It takes time for the L-dopa to get absorbed through the gut and then into the brain. Usually about 15-30 minutes.
How Long Does DA Remain in Your System?

- The “half-life” is the amount of time it takes for ½ of the l-dopa to be cleared from your system.
- This is not changed significantly as the disease progresses.
- In early disease, dopamine can be stored in the neurons so benefit from carbidopa/levodopa lasts longer than the half-life.
In Early Disease, Carbidopa/levodopa can be taken at 5-7 hour intervals

Dopamine neurons can store dopamine. In early disease, patients are not so dependent on the fluctuations in l-dopa levels in the brain. As more DA neurons are lost, this “buffering” capacity is lost.
The Levodopa \textit{Therapeutic Window} Narrows with Disease Progression

The therapeutic window narrows with disease progression. In early disease, the therapeutic window is wider, allowing for a better balance between efficacy and dyskinesia. As the disease progresses to moderate and advanced stages, the therapeutic window narrows, making it more challenging to maintain an effective dose. This is due to the increased risk of dyskinesia at higher levodopa concentrations and the reduced efficacy at lower concentrations.

\textbf{Obeso et al. 2000}
How Common are Motor Fluctuations?

- Older (fluctuations)
- Older (dyskinesias)
- Younger (fluctuations)
- Younger (dyskinesias)

Duration of Levodopa Treatment (years)

% Patients
What Can Be Done to Reduce Risk of Developing Motor Fluctuations and Dyskinesias?
The ELLDOPA Study

- 361 early PD patients
- Randomized, double-blind, placebo-controlled
- 40 week trial

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo 150 mg/day</th>
<th>Levodopa 300 mg/day</th>
<th>Levodopa 600 mg/day</th>
<th>P-value (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, N</td>
<td>90</td>
<td>92</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>3 (3.3)</td>
<td>3 (3.3)</td>
<td>2 (2.3)</td>
<td>15 (16.5)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>19 (21.1)</td>
<td>19 (20.1)</td>
<td>14 (15.9)</td>
<td>12 (13.2)</td>
</tr>
<tr>
<td>Freezing</td>
<td>13 (14.4)</td>
<td>9 (9.8)</td>
<td>6 (6.8)</td>
<td>5 (5.5)</td>
</tr>
<tr>
<td>On-Off</td>
<td>3 (3.3)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Wearing-Off</td>
<td>12 (13.3)</td>
<td>15 (16.3)</td>
<td>16 (18.2)</td>
<td>27 (29.7)</td>
</tr>
</tbody>
</table>

- Keep levodopa dose below 600 mg/day advisable to avoid motor fluctuations

Factors Predictive of the Development of Levodopa-Induced Dyskinesia and Wearing-Off in Parkinson’s Disease

Young age at Onset
Higher L-dopa dose
Low body weight
North Americans
Entacapone
Female gender
More severe symptoms

(Olanow et al 2013)
Dopamine Agonists Bind to DA Receptors

**Advantages**
- Longer ½ life: 6 hours
- No competition to get absorbed through gut or into brain
- Do not need to be converted
- Extended Release Formulations

**Disadvantages**
- Not as powerful as l-dopa
- Worse side effects
  - Nausea, tiredness, confusion, hallucinations, orthostatic hypotension, impulse control

Ropinirole (Requip ®)

Pramipexole (Mirapex ®)

Rotigotine (Neupro ®)
• Double-blind, 5 year controlled study of L-dopa vs pramipexole
• Reduced risk of dyskinesias in pramipexole group.

Study flaw:
L-dopa patients better treated throughout study.

JAMA 2000
Dopamine agonists in the treatment of early Parkinson’s disease: A meta-analysis

William L. Baker\textsuperscript{a,b}, Dee Silver\textsuperscript{c}, C. Michael White\textsuperscript{a,b}, Jeffrey Kluger\textsuperscript{d}, Jeffrey Aberle\textsuperscript{a,b}, Aarti A. Patel\textsuperscript{e}, Craig I. Coleman\textsuperscript{a,b,*}

- 25 randomized controlled trials
- DA agonists inferior to L-dopa in treating motor symptoms (2 point higher ADL score and 4 point higher motor score)
- DA agonists result in lower rate of motor fluctuations
- Adverse effects worse in DA agonists with 17.2% withdrawal rate vs 8.8% for L-dopa treated patients
DA Agonists

• Less effective vs l-dopa
• Perhaps less risk motor complications
• Probably no long term benefit vs l-dopa
• More side effects
  – Somnolence
  – Leg edema (up to 45%)
  – Constipation
  – Dizziness; hypotension
  – Hallucinations
  – Nausea
  – Impulse control disorders (6-25%)
  – Punding
• 782 patients, randomized, open label*
  – L-dopa
  – Bromocriptine (a dopamine agonist)
• Endpoints: Mortality, disability, motor complications
• Long term outcomes similar with respect to mortality and motor complications. L-dopa group had sustained better motor functioning

*L-dopa + selegiline arm stopped prematurely due to increased mortality; not confirmed in other studies
Initiating Medication Therapy in Early PD

- Consider MAOb-inhibitor (selegiline, rasagiline)*
- Consider DA agonist (pramipexole, ropinirole, rotigotine)
- Prescribe l-dopa at minimum dose needed to provide control of symptoms (usually 300-400 mg/day at about 5 hour intervals)
- Evaluate efficacy at 3 months

*Safinamide not indicated as monotherapy
What Can Be Done to Treat Motor Fluctuations and Dyskinesias?
Therapeutic Window

- With advancing disease, people become dependent on fluctuations of L-dopa levels.
- If the level is too low, symptoms are not treated. If the levels are too high, dyskinesias result.
Strategies to Keep DA Stimulation Steady

- **Shorten Dosing Interval**
- **Add Helper Medication**
  - COMT inhibitors
    - Entacapone (Comtan®)
  - MAO-b inhibitors
    - Selegiline, Rasagiline, Safinamide
- **Add Dopamine Agonist**
  - Ropinirole (Requip®)
  - Pramipexole (Mirapex®)
  - Rotigotine patch (Neupro®)
- **Long-acting carbidopa/levodopa: Rytary**
- **Apomorphine injections**
- **Continuous Infusion of l-dopa: duopa**
Taking Medications at Shorter Intervals Leads to More Steady DA Levels
Strategies to Keep DA Stimulation Steady

• Shorten Dosing Interval

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  – COMT inhibitors
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• Apomorphine

• Continuous Infusion of L-dopa
Helper Medications Make Dopamine Last Longer by Blocking Enzymes Which Break it Down*

**COMT inhibitors** block COMT

**MAOb inhibitors** block monoamine oxidase

Dopamine is broken down by two enzymes. If the enzymes are blocked, the dopamine lasts longer.

Helper medications add about 20 minutes of “on” time per dose of levodopa.

*COMT inhibition also works outside the brain to block breakdown of l-dopa*
Strategies to Keep DA Stimulation Steady

• Shorten Dosing Interval
• Add Helper Medication
  – COMT inhibitors
    • Entacapone (Comtan®)
  – MAOb inhibitors
    • Selegiline, Rasagalone (Azilect®)
• Add Dopamine Agonist
  – Ropinirole (Requip®)
  – Pramipexole (Mirapex®)
  – Rotigotine patch (Neupro®)
• Apomorphine
• Continuous Infusion of L-dopa
Dopamine Agonist as Add-on Therapy

Dopamine agonists have more side effects than levodopa and should not be used in persons who are “older”, have cognitive problems, hallucinations/delusions or low blood pressure.
Strategies to Keep DA Stimulation Steady

• Shorten Dosing Interval

• Add Helper Medication
  – COMT inhibitors
    • Entacapone (Comtan®)
  – MAOβ inhibitors
    • Selegiline, Rasagiline (Azilect®)

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• Long-acting carbidopa/levodopa: Rytary

• Apomorphine

• Continuous Infusion of L-dopa: duopa
Rytary

- Extended release capsule formulation of carbidopa/levodopa in a 1:4 ratio
- Contains both immediate and extended release components
- Dose often has to be “tweaked”
**Crossover Comparison of IPX066 and a Standard Levodopa Formulation in Advanced Parkinson’s Disease**

<table>
<thead>
<tr>
<th></th>
<th>Rytary</th>
<th>Carbidopa/ Levodopa IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td>2.0 +/- 1.1</td>
<td>0.87 +/- 0.5</td>
</tr>
<tr>
<td>Time to reach 50% Cmax (h)</td>
<td>0.78 +/- 0.40</td>
<td>0.76 +/- 0.47</td>
</tr>
<tr>
<td>Duration above 50% Cmax</td>
<td>4.0 +/- 2</td>
<td>1.4 +/- 0.7</td>
</tr>
</tbody>
</table>

Half-life

![Graph showing Cmax and Time (hrs) over 10 hours](image)

**Movement Disorders, 2011**
Strategies to Keep DA Stimulation Steady

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  – Ropinirole (Requip®)
  – Pramipexole (Mirapex®)
  – Rotigotine patch (Neupro®)
• Long-acting carbidopa/levodopa: Rytary
• Apomorphine
• Continuous Infusion of L-dopa: duopa
Apomorphine (Apokyn)

- Dopamine agonist administered subcutaneously
- Indicated for acute, intermittent “off” episodes
- Effective for about an hour
- Helpful first in AM, unexpected off times, security blanket
Strategies to Keep DA Stimulation Steady

- **Shorten Dosing Interval**
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  - Rotigotine patch (Neupro®)
- **Apomorphine**
- **Continuous Infusion of L-dopa (Duopa)**
The Duopa Pump Can Theoretically Keep Dopamine Constant
Duopa is Superior to Oral Levodopa in Reducing Off Time but There are Some Risks

(Olanow et al 2014)
Management of Dyskinesias

- Take smaller but more frequent doses of levodopa
- Amantadine, Amantadine ER (Gocovri)
- Deep Brain Stimulation
Amantadine

• Has inhibitory effects against influenza virus; indicated as anti-viral agent in 1960’s
• Tried in PD in and found to help PD motor symptoms
• Began to be used to treat dyskinesias in 1990’s
• Thought to antagonize glutamate NMDA receptors and cholinergic muscarinic receptors, thought to play a role in development of dyskinesias. Also increases dopamine synthesis
Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson’s disease

- Double-blind, placebo-controlled, cross-over study
- Eighteen patients with advanced PD
- Patients received 100 mg, 3-4 times per day
- Evaluated during an IV levodopa infusion, along with carbidopa
- Subsequent studies confirmatory
- Benefit persists over time (Ory-Magne et al 2014)

(Verhagen et al 1998)
Amantadine: Adverse Effects

- Neuropsychiatric
- Withdrawal syndrome
- Serotonin Syndrome
- Impulse Control Disorders?
- Orthostatic hypotension
- Livedo reticularis (40%)
- Corneal problems
- Peripheral edema
- Somnolence
Amantadine ER (Gocovri)

- Long-acting formulation
- Taken once daily at bedtime
- Formulated to slowly rise during sleep achieving high levels during waking hours
- May be better tolerated than Amantadine IR

(Perez-Lloret 2018)
Conclusions/Summary

- Motor complications (fluctuations & dyskinesias) are a part of advancing PD.
- We have tools to manage motor complications pharmacologically.
- For those patients where we cannot successfully manage motor complications, Deep Brain Stimulation is an option.