Parkinson Disease
Levodopa-Induced Dyskinesia

Christopher Kenney, MD
Novartis Pharmaceuticals
Disclosures

• Dr. Kenney is a full-time employee of Novartis Pharmaceuticals Corporation

• The opinions expressed in this presentation are solely those of Dr. Kenney and not necessarily those of Novartis Pharmaceuticals Corporation
Overview

• Introduction: Parkinson disease epidemiology/indications/disease progression
• Clinical presentation of PD-LID
• Impact of PD-LID: QoL & financial burden
• Treatments for PD-LID
• Methodology
  – Outcome variables: differing effect sizes
  – Challenges: MCIC, worsening PD, con meds
Introduction

• 1 million PD patients in US (~200,000 with LID)
• Existing Parkinson’s disease indications
  – Drug X “is indicated for the treatment of the signs and symptoms of idiopathic Parkinson’s disease as initial monotherapy and as adjunct therapy to levodopa”.
• No drug is currently approved for Parkinson’s Disease Levodopa-Induced Dyskinesia (PD-LID)
  – However, several small/medium studies (n<70) have demonstrated efficacy using amantadine
Introduction

Hawkes et al 2009
Introduction

- The pathophysiologic mechanisms responsible for PD-LID are not fully understood, though both severity of dopamine neuron loss and chronic administration of a drug with a short half-life, such as levodopa, are of critical importance.

Jankovic 2005; Encarcion & Hauser 2008; Hely et al. 2005
Clinical Presentation

• ON PD-LID
  – Peak dose dyskinesia (70-80%)
  – Diphasic dyskinesia (10-20%)
  – Dystonia: abnormal/painful postures

• OFF PD-LID
  – Dystonia (typically early morning)

Jankovic 2005
Severe Peak Dose PD-LID
Mild Peak Dose PD-LID
OFF Dystonia
PD-LID/Impact

• >90% of PD patients have PD-LID by 15 years
  – Half of these patients considered it disabling
• PD-LID adversely impacts several domains of QoL (PDQ39 scale)
  – mobility, ADLs, stigma, emotional well-being, bodily discomfort and communication
• Increasing severity of dyskinesias is associated with increasing depression and increased falls

PD-LID/Impact

• PD-LID may prevent the ability to increase PD medications to improve motor function

• Financial burden
  – Total medical expenses for PD treatment in the US are estimated to be 23 billion USD annually
    • 19-23K USD per patient annually
  – After patients develop PD-LID, treatment costs increase from ~18K to 26K USD

Suh et al 2012; Encarnacion & Hauser 2008
PD-LID Treatment

- Prevention: CALM-PD (pramipexole vs levodopa)
  - Patients with PD-LID:

<table>
<thead>
<tr>
<th>End Points</th>
<th>Pramipexole (n = 151)</th>
<th>Levodopa (n = 150)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dopaminergic complications‡</td>
<td>42 (27.8)</td>
<td>76 (50.7)</td>
<td>0.45 (0.30-0.66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Wearing off</td>
<td>36 (23.8)</td>
<td>57 (38.0)</td>
<td>0.57 (0.37-0.88)</td>
<td>.01</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>15 (9.9)</td>
<td>46 (30.7)</td>
<td>0.33 (0.18-0.60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>On-off fluctuations</td>
<td>2 (1.3)</td>
<td>8 (5.3)</td>
<td>0.27 (0.06-1.32)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Parkinson Study Group 2000
PD-LID Treatment

• Treatment to reduce severity
  – Various strategies may help with approved drugs (lower/more frequent levodopa doses, higher dopamine agonist dose)
  – Marketed: amantadine, clozapine, quetiapine
  – In development: fipamezole, safinamide, mavoglurant, dipraglurant
  – Surgical: Deep brain stimulation/apomorphine pump/Intra-duodenal levodopa therapy

Pahwa et al. 2006; Ferreira et al 2012; Gottwald et al. 2011
• Several PD-LID clinical scales available
  – Unified Dyskinesia Rating Scale (UDysRS)
  – Modified Abnormal Involuntary Movement Scale (mAIMS)
  – Lang Fahn Activities of Daily Living Dyskinesia Scale (LF)
  – 26-Item Parkinson Disease Dyskinesia scale (PD26)
  – Unified Parkinson’s Disease Rating Scale
  – Patient reported diaries
Background: MJ Fox Foundation study to validate dyskinesia rating scales using amantadine; determine effect sizes for each scale to establish a bar against which new treatments can be compared to amantadine

Study design: randomized, placebo-controlled trial of amantadine 200 mg bid, assessing dyskinesia at baseline, four and eight weeks using the following scales:

- Dyskinesia Rating Scale (UDysRS)
- Lang-Fahn Activities of Daily Living Dyskinesia Rating Scale (LF)
- 26-Item Parkinson’s Disease Dyskinesia scale (PD26)
- patient reported diaries
- modified Abnormal Involuntary Movements Scale (mAIMS)
- Rush Dyskinesia Rating Scale (RDRS)
- Movement Disorder Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)
- Clinical Global Impression of Change (CGI-C)

n=31 amantadine; n=30 placebo completing the study

Goetz et al. 2013 (in press)
<table>
<thead>
<tr>
<th>Scale</th>
<th>Effect Size (eta2)</th>
<th>Effect Size (Cohen’s D) Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDysRS Total</td>
<td>0.138</td>
<td>~0.8</td>
</tr>
<tr>
<td>CGI-C</td>
<td>0.096</td>
<td>~0.7</td>
</tr>
<tr>
<td>Lang-Fahn</td>
<td>0.086</td>
<td>~0.6</td>
</tr>
<tr>
<td>PD-26</td>
<td>0.086</td>
<td>~0.6</td>
</tr>
<tr>
<td>mAIMS</td>
<td>0.061</td>
<td>~0.5</td>
</tr>
<tr>
<td>RDRS</td>
<td>0.003</td>
<td>~0.1</td>
</tr>
<tr>
<td>Patient reported diaries</td>
<td>0.003</td>
<td>~0.1</td>
</tr>
<tr>
<td>MDS-UPDRS – Questions 4.1, 4.2, 4.6</td>
<td>0.002</td>
<td>~0.1</td>
</tr>
</tbody>
</table>

- Eta2 effect sizes:
  - .01 ~ small effect size
  - .06 ~ medium effect size
  - .14 ~ large effect size

- Cohen’s D Effect sizes
  - 0.3 ~ small effect size
  - 0.5 ~ medium effect size
  - 0.8 ~ large effect size

Goetz et al. 2013 (in press)
• Unified Dyskinesia Rating Scale
  – New rating scale designed to capture the essential features of PD-LID
  – Incorporates elements from other PD-LID scales and input from patient/caregiver focus groups
  – Acceptable levels of internal consistency and inter- and intra-rater reliability

Goetz et al. 2008
• Unified Dyskinesia Rating Scale (Four parts)
  – I: Historical Disability (patient perceptions) of On-Dyskinesia impact
  – II: Historical Disability (patient perceptions) of Off-Dystonia impact
  – III: Objective Impairment (dyskinesia severity, anatomical distribution over seven body regions, and type (choreic or dystonic) based on four activities observed or video-recorded
  – IV: Objective Disability based on Part III activities

Goetz et al. 2008
PD-LID/Methodology

- Challenges: Minimal Clinically Important Change
  - Not established for PD-LID, only PD motor function

<table>
<thead>
<tr>
<th>Publication</th>
<th>Population</th>
<th>MID</th>
<th>Baseline Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schrag et al, 2006</td>
<td>Early PD</td>
<td>5 points (UPDRS III)</td>
<td>22 points (UPDRS III)</td>
</tr>
<tr>
<td>Rascol, 2006</td>
<td>Early PD (Compared two studies)</td>
<td>A) 1.5 points (UPDRS III)</td>
<td>17.8 points (UPDRS III)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B) 6.4 points (UPDRS III)</td>
<td>24.0 points (UPDRS III)</td>
</tr>
<tr>
<td>Shulman et al, 2010</td>
<td>Early PD</td>
<td>2.5 points (UPDRS III)</td>
<td>27.2 points (UPDRS III)</td>
</tr>
<tr>
<td>Hauser et al, 2011</td>
<td>Early PD</td>
<td>2.4 points (UPDRS III)</td>
<td>17.8 points (UPDRS III)</td>
</tr>
<tr>
<td>Hauser et al, 2011</td>
<td>Advanced PD</td>
<td>1 hour OFF time (patient diary)</td>
<td>6.1 hour OFF (patient diary)</td>
</tr>
</tbody>
</table>

PD-LID/Methodology

- Challenges
  - Developing drugs that don’t worsen parkinsonism
  - Defining population: severity, optimized meds
  - Keeping other concomitant PD medications stable
  - Evaluating whether improved PD-LID allows physicians to optimize other PD medications
  - Demonstrating maintenance of effect for a sufficient duration of time
  - Evaluating for potential withdrawal effects
• Impact: PD-LID is common, adversely impacts QoL and causes increased medical costs
• Treatments: several options available but no treatment is yet approved for PD-LID
• Methodology
  – UDysRS appears to be best clinical scale
• Challenges: defining MCIC, ensuring underlying disease does not worsen, and evaluating whether treatments permit levodopa optimization