Disease Progression in Parkinson’s Disease – Evidence for Protective Effects of Drug Treatment

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Clinical Pharmacology

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Disease Progress + Drug Action
Old Model - New Meaning

\[ E = E_0 + \frac{E_{\text{max}} \cdot \text{Conc}}{EC50 + \text{Conc}} \]

Disease Progress

Drug Action
Drug Action Symptomatic

\[
E(t) = \frac{E \text{ max}(t) \cdot C_{e_{LD}}(t)}{E \text{D50} + C_{e_{LD}}(t)}
\]

\[
E \text{ max}(t) = E \text{ max}_0 + BEML \cdot \left(1 - \exp\left(\frac{\ln(2)}{T \text{EML}} \cdot t\right)\right)
\]

CeLD(t) = Effect compartment LD ‘concentration’
E(t) = Effect at daily levodopa dose LD
E_{max_0} = Baseline Max symptomatic effect of levodopa
ED50 = LD producing 50% of E_{max}(t)
BEML = E_{max} change at steady state
TEML = Half-life of E_{max} change time

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Disease Progress and Drug Action

Linear
\[ \frac{dS}{dt} = \alpha \cdot f(Rx) \]

Exponential
\[ \frac{dS}{dt} = \frac{\ln(2)}{T_{prog}} \cdot (S_{ss} \cdot f(Rx) - S) \]

Gompertz
\[ \frac{dS}{dt} = \frac{\ln(2)}{T_{prog} \cdot f(Rx)} \cdot (S_{ss} - S) \cdot S \]

\( \alpha \) = Linear progression rate  
\( T_{prog} \) = Progression ‘half-life’  
\( S_{ss} \) = Asymptotic ‘burnt out’ steady state
Protective Drug Action & Interaction

Levodopa \[ FPLD = \exp(KPL \cdot C_{LD}(t)) \]

Deprenyl \[ FPDP = \exp(KPD \cdot C_{DP}(t)) \]

\[ \theta(LD, DP) = \theta_0 \cdot FLXD \cdot FPLD \cdot FPDP \]

\[ C_{LD}(t) = \text{Css levodopa at time } t \]
\[ KPL = \text{Levodopa protective parameter} \]
\[ C_{DP}(t) = \text{Css deprenyl at time } t \]
\[ KPD = \text{Deprenyl protective parameter} \]
\[ FLXD = \text{Levodopa * Deprenyl interaction} \]
\[ \theta_0 = \text{Untreated progression parameter} \]
Disease Progress Models

<table>
<thead>
<tr>
<th>Progress Model</th>
<th>Obj</th>
<th>SigDig</th>
<th>S0 U</th>
<th>α U/Year</th>
<th>Sss U</th>
<th>Tprog Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gompertz Tprog</td>
<td>76306</td>
<td>3.7</td>
<td>21.8</td>
<td>.</td>
<td>94</td>
<td>117</td>
</tr>
<tr>
<td>Gompertz Sss</td>
<td>76366</td>
<td>3</td>
<td>21.9</td>
<td>.</td>
<td>140</td>
<td>227</td>
</tr>
<tr>
<td>Linear Alpha</td>
<td>76638</td>
<td>5.9</td>
<td>21.4</td>
<td>12.1</td>
<td>.</td>
<td>.</td>
</tr>
</tbody>
</table>

Best model is Gompertz with Drug Action on Tprog
Gompertz Disease Progress

![Graph showing Gompertz Disease Progress with different treatments: Gompertz Levodopa, Gompertz Levodopa+Deprenyl, Gompertz, and Linear.](Graph.png)

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Wash-Out Study
Hauser et al.

- Washout observed for 15 days after withdrawal of Levodopa or Bromocriptine
- Some patients had previously been withdrawn from Deprenyl 2 months prior to washout
- 31 Patients Evaluated by 20 Neurologists
  - 35% (11) No Washout
  - 23% (7) Complete Washout
  - 32% (10) Incomplete Washout
  - 10% (3) Uncertain if Complete
- 20 Patients with Washout Were Modelled


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Levodopa Washout

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Washout Predictions

Fast=Complete by 2 weeks  Slow=5.65 day half-life

Incomplete At 14 days
ELLDOPA Study

ELLDOPA – Earlier vs Later L-DOPA

Control
• Placebo

Levodopa
• Low dose - 0.15 g/day
• Medium dose - 0.3 g/day
• High dose - 0.6 g/day

Group size - 90 patients per group

Fahn S. Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Earlier vs Later L-DOPA. Archives of Neurology 1999;56(5):529-35

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Predicted ELLDOPA Effects

ELLDOPA assumes all symptomatic effect is washed out at 2 weeks

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ELLDOPA Power
Null Hypothesis LD=Placebo α=0.05

<table>
<thead>
<tr>
<th>Drug Action</th>
<th>Washout of symptomatic benefit</th>
<th>Power (%) ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>Fast</td>
<td>7 ± 3</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>Symptomatic + Protective</td>
<td>Fast</td>
<td>86 ± 3</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>100 ± 0</td>
</tr>
</tbody>
</table>
Does Levodopa Affect Parkinson’s Progression?

Design - Clear

Results - Murky

Fahn S. ELLDOPA results presented at Movement Disorder Society meeting, Miami, FL, November. 2002
Predicted & Observed

UPDRS total Mean Difference from Placebo
Reported ELLDOPA Observations
100 Simulated Trial Replications ± SD

<table>
<thead>
<tr>
<th>Levodopa Protective</th>
<th>Low 150 mg/d</th>
<th>Medium 300 mg/d</th>
<th>High 600 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed Primary</td>
<td>5.9</td>
<td>5.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Observed Secondary</td>
<td>5.1</td>
<td>5.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Predicted Slow Washout</td>
<td><strong>5.4 ± 1.3</strong></td>
<td><strong>7.2 ± 1.6</strong></td>
<td><strong>8.7 ± 1.6</strong></td>
</tr>
</tbody>
</table>

Observed difference too big for protective effect alone?
What Happened in ELLDOPA?

The graph shows the progression of UPDRS scores over time in different groups:

- **Protective 75%**: This group has a 75% protective effect on UPDRS scores.
- **Symptomatic 25%**: This group shows a 25% increase in UPDRS scores.

The graph includes the following key points:

- **Washout Starts**: At 280 days, the washout process begins.
- **UPDRS observed**: At 300 days, the UPDRS scores are observed.
- **UPDRS**: The scale ranges from 12 to 32.

The chart indicates that the washout process starts at 280 days and the UPDRS scores are observed at 300 days, with distinct lines for Protective 75% and Symptomatic 25% groups.
Clinical Pharmacology and Disease Progress

• Describes changes in drug action over time
  – Emax increase in UPDRS
• Interprets clinical trial outcome
  – ELLDOPA protective + washout
• Explains clinical experience
  – Treatment becomes less effective but it’s actually the disease not the drug