Neuroprotection in PD: ADAGIO, PROUD PD, Elldopa & Urate

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‘there appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped’

James Parkinson, 1817
MODIFYING PARKINSON’S DISEASE

REDUCE MOTOR COMPLICATIONS
- Early DA Therapy
- Continuous Dopaminergic Stim
- Deep Brain Stimulation
- Anti-dyskinesia drugs
  - amantadine, dopamine transport inhib, gaba and glutamatergic drugs

SLOW DISEASE PROGRESSION
- Block Neurodegenerative process
  - oxidative stress
  - protein aggregation
  - apoptosis, necrosis

LIMIT COGNITIVE AND NON-DOPAMINERGIC SYMPTOMS
- Dementia
- Depression
- Postural Instability
- Freezing
- Autonomic failure

Restorative Therapies
- cells, genes, trophic factors
Levodopa Extends Lifespan

- Comparison of longevity in pre- and post-levodopa treatment patients revealed that patients treated with levodopa had less excess mortality than non-levodopa treated patients.

Sweet et al., Ann Int Med 1975:83;456-463
# Neuroprotective Trials in PD

<table>
<thead>
<tr>
<th>Class</th>
<th>Trial</th>
<th>N°</th>
<th>Primary outcome</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiapoptotic agents</td>
<td>Olanow et al. [42]</td>
<td>301</td>
<td>Time to symptomatic treatment</td>
<td>12–18 months</td>
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<tr>
<td>-TCH346</td>
<td>PRECEPT [45]</td>
<td>806</td>
<td>Time to symptomatic treatment</td>
<td>Terminated after ~21 months</td>
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<tr>
<td>-CEP-1347</td>
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<td>Change in total UPDRS</td>
<td>12 months</td>
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<tr>
<td>-Minocycline</td>
<td>NINDS NET-PD FS-1 [47]</td>
<td>200</td>
<td>Change in total UPDRS</td>
<td>12 months</td>
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<tr>
<td>Antioxidants</td>
<td>DATATOP [73]</td>
<td>800</td>
<td>Time to symptomatic treatment</td>
<td>Terminated after ~12 months</td>
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<td>-Vitamin E</td>
<td>QE2 [5]</td>
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<td>Change in total UPDRS</td>
<td>16 months</td>
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<tr>
<td>-Coenzyme Q10</td>
<td>NINDS NET-PD FS-Too [62]</td>
<td>213</td>
<td>Change in total UPDRS</td>
<td>12 months</td>
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<tr>
<td>-Creatine</td>
<td>Bender et al. [72]</td>
<td>60</td>
<td>123I-β-CIT SPECT changes</td>
<td>24 months</td>
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<tr>
<td>Glutamate antagonists</td>
<td>NINDS NET-PD FS-1 [47]</td>
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<td>Change in total UPDRS</td>
<td>12 months</td>
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<tr>
<td>-Ranolazine</td>
<td>Jankovic and Hunter [88]</td>
<td>20</td>
<td>Change in UPDRS II and III</td>
<td>6 months</td>
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<td>-Ropinirole</td>
<td>REAL-PET [32]</td>
<td>186</td>
<td>Time to symptomatic treatment</td>
<td>Prematurely terminated</td>
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<tr>
<td>-α-dihydroergocryptine</td>
<td>Pöpperl et al. [79]</td>
<td>25</td>
<td>123I-β-CIT SPECT changes</td>
<td>46 months</td>
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<tr>
<td>Levodopa</td>
<td>Jankovic and Hunter [88]</td>
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<td>18F-DOPA PET changes</td>
<td>24 months</td>
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<tr>
<td>-Levodopa</td>
<td>REAL-PET [32]</td>
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<td>123I-IPT SPECT changes</td>
<td>52 weeks</td>
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<tr>
<td>MAO inhibitors</td>
<td>DATATOP [73]</td>
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<td>Change in UPDRS</td>
<td>Terminated after ~12 months</td>
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<td>-Selegiline</td>
<td>Tetrud and Langston [99]</td>
<td>54</td>
<td>Time to symptomatic treatment</td>
<td>3 years</td>
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<td>-Deprenyl</td>
<td>SINDEPAR [102]</td>
<td>101</td>
<td>Change in total UPDRS</td>
<td>14 months</td>
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<tr>
<td>-Lazabemide</td>
<td>Swedish Parkinson Study Group [100]</td>
<td>157</td>
<td>Time to symptomatic treatment</td>
<td>1–3 years</td>
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<tr>
<td>Neuroimmunophilin ligands</td>
<td>Norweigan–Danish Study Group [103]</td>
<td>79</td>
<td>Change in total UPDRS</td>
<td>60 months</td>
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<tr>
<td>Neurotrophic factors</td>
<td>TEMPO [7]</td>
<td>404</td>
<td>Change in total UPDRS</td>
<td>12 months</td>
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<td>-GDNF</td>
<td>NIL-A phase II clinical trial [111]</td>
<td>300</td>
<td>Change in UPDRS motor score</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>NINDS NET-PD FS-To [62]</td>
<td>213</td>
<td>Change in total UPDRS</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>ICV GDNF Study Group [117]</td>
<td>50</td>
<td>Change in UPDRS motor score</td>
<td>8 months</td>
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<tr>
<td></td>
<td>Lang et al. [119]</td>
<td>34</td>
<td>Change in UPDRS motor score</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Lohle et al., J Neurol Sci 2010;289:104–14
Developing Neuroprotective Therapies for Neurodegenerative Diseases: Issues and Challenges

- Etiology of the disease is still unknown/uncertain
- Animal models do not reliably or fully recapitulate the clinical disease
- Clinical trials require large numbers of patients, long duration
- Minimal or non-validated “biomarkers” of impact on disease progression
- Regulatory requirements for ‘disease-modifying’ indication are uncertain
Of Mice and Men

- Mouse substantia is not nigra – not pigmented
- Presumably equal expression of α-synuclein does not lead to aggregation/neuronal demise in mice as it does in humans
- Mouse lifespan much shorter – most studies ignore the seemingly essential effects of aging
- A53T α-synuclein mutation in humans is the normal sequence in a mouse
ADAGIO Trial

- Delayed-start design with four arms, either early or delayed administration of two doses (1mg, 2mg) of rasagiline
- 1,146 subjects vs. 404 in TEMPO trial
- 9 months for both arms of study vs. 6 months in TEMPO
- 3 Endpoints vs. 1 in TEMPO

Olanow et al., NEJM 2009;361:1268-78
ADAGIO Endpoints

Olanow et al., NEJM 2009;361:1268-78
ADAGIO Trial Results

- 1mg dose met all 3 endpoints
  - Baseline to end change in UPDRS
  - Slope of curves in weeks 12-36
  - Non-inferiority in slope of weeks 48 to 72
- 2mg dose met none
Problems with Interpretation of ADAGIO

- Possibly biased sample due to selection of patients likely to ‘survive’ placebo phase of study
- Using UPDRS, especially ‘old’ UPDRS has problems
  - Not very sensitive to early changes in symptoms
  - Subjective
  - Likely not linear progression
- Difference between early and delayed start groups (about 2 UPDRS total points) was only about 1% of total
- **Failure or 2mg dose to meet any endpoints**

Adapted from Ahlskog and Uitti *Neurology* 2010;74;1143-1148
Why didn’t 2mg work?

Possible Explanations

• Symptomatic benefit masked disease-modifying effect
  – But, symptomatic effect was equal between doses in first phase
  – MAO-B nearly completely inhibited at both doses

• Disease modifying effect may be independent of MAO-B inhibition and more potent at lower doses
  – But propargylamine compound TCH346 failed in large Trial
Other Problems

- Variability in response to rasagilin was twice the magnitude of the positive finding of the study:
  - Delayed-start, active phase 2mg: +1.16 pts
  - Delayed-start, active phase 1mg: -0.23
  - Early-start, first phase 2mg: -1.11
  - Early-start, first phase 1mg: -1.26
  - Early-start, second phase 1mg: -1.56
  - Early-start, second phase 2mg: -2.36
  
  Range: 3.52 pts

  1mg delayed start – 1mg early start: 1.68 pts

- Design assumed that symptomatic effect would plateau by 12 weeks, but this does not seem to be the case.

- Does rasagilin even do better than levodopa?
Adagio vs. Elldopa

Fahn et al. NEJM 2004;351: 2498-508
The PROUD Study
Pramipexole on Underlying Disease

- 535 de novo PD patients – 411 in primary comparison
- Primary outcome was change from baseline in total UPDRS
  - No difference between pramipexole and placebo
- Secondary outcomes:
  - PDQ39 – not significantly different
  - DATSCAN – not significantly different

The Urate Story

• Serum urate elevation has been shown to reduce risk of PD

• Schwarzschild et al. showed that higher levels of serum and CSF urate predicted slower rate of progression in PD from DATATOP and PRECEPT study data

• Safety trial of inosine, which is precursor of urate, SURE PD, is underway

Schwarzschild et al., Arch Neurol 2008;65:716-22
Where to go from here?

- Recognize the limitations of relying on models utilizing acute toxic injuries
- Reconsider delayed start trial design
- Consider novel ways to model outcomes
- Replace UPDRS with quantitative assessments

<table>
<thead>
<tr>
<th>Potential neuroprotective drugs</th>
<th>GM-1 ganglioside&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid</td>
<td>Minocycline&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Modafinil</td>
</tr>
<tr>
<td>Azulenyl nitrone</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Caffeine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Coenzyme Q10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pramipexole&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>COX I-II inhibitors</td>
<td>Ropinirole&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Rasagiline&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Erythropoietin</td>
<td>Remacemide</td>
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<tr>
<td>Estrogen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Selegiline&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Folate</td>
<td>GM-1 ganglioside&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>GPI-1485&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Candidates for near-term Phase II or III neuroprotection studies.
Re-analysis of DATATOP data

Natural history

300mg levodopa

300mg levodopa and selegiline

Holford et al., *J Pharmacokinetics and Pharmacodynamics* 2006;33:281-311
Conclusions

- We have no proven neuroprotective therapies in Parkinson’s disease.
- We may not get them unless:
  - We develop a better understanding of the pathophysiology of PD
  - We develop better animal models
  - We develop better biomarkers of progression
  - We develop better trial designs
- Nonetheless, we want to try another agent based upon current notions of PD pathophysiology, tested in current models of PD in a somewhat novel trial design, because we have HOPE.