Medications in the treatment of Parkinson’s disease

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WLA VA Medical Center
Idiopathic Parkinson’s Disease

- 2nd most common neurodegenerative disorder
  - lifetime risk: 1 in 40
- Age of onset
  - Common after 60 y/o
  - Young onset (20-50 y/o)
- Men get it more often than women
# Parkinson’s Disease Genes

<table>
<thead>
<tr>
<th>Name and Locus</th>
<th>Gene</th>
<th>Mode of Inheritance; Pathological Features</th>
<th>Protein Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARK1 4q21-q22</td>
<td>α-synuclein</td>
<td>AD Lewy bodies</td>
<td>synaptic vesicle trafficking</td>
</tr>
<tr>
<td>PARK2 6q25.2-q27</td>
<td>Parkin</td>
<td>AR (AD?) no Lewy bodies</td>
<td>Ubiquitin E3 ligase,</td>
</tr>
<tr>
<td>PARK3 2p13</td>
<td>Unknown</td>
<td>AD Lewy bodies</td>
<td></td>
</tr>
<tr>
<td>PARK4 4q21</td>
<td>triplication α -syn</td>
<td>AD Lewy bodies</td>
<td></td>
</tr>
<tr>
<td>PARK5 4p14</td>
<td>UCH L1</td>
<td>AD ?</td>
<td>Removes polyubiquitin</td>
</tr>
<tr>
<td>PARK6 1p35-p36</td>
<td>PINK1</td>
<td>AR ?</td>
<td>PTEN-induced kinase 1 (mito localized, protects UPS inhib)</td>
</tr>
<tr>
<td>PARK7 1p36</td>
<td>DJ-1</td>
<td>AR ?</td>
<td>Sumoylation pathway</td>
</tr>
<tr>
<td>PARK8 12q12</td>
<td>LRRK2</td>
<td>AD Lewy bodies</td>
<td>Kinase. GTPase</td>
</tr>
<tr>
<td>PARK9 1p36</td>
<td>ATP13A2</td>
<td>AR ?</td>
<td>Lysosomal ATPase</td>
</tr>
<tr>
<td>PARK10 1p32</td>
<td>Unknown</td>
<td>? Dominant</td>
<td></td>
</tr>
<tr>
<td>PARK11 2q34</td>
<td>Unknown</td>
<td>AD reduced pen ?</td>
<td></td>
</tr>
<tr>
<td>PARK12 Zq21</td>
<td>Unknown</td>
<td>X-linked ?</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of Parkinson’s Disease

- Nonpharmacologic
  - Education
  - Exercise

- Medications
  - Neuroprotective
  - Symptomatic

- Surgical
  - DBS, transplantation
NARROWING THERAPEUTIC WINDOW WITH TIME

L-DOPA

dyskinesia

bradykinesia

years

therapeutic window
Motor Fluctuations and Age

Dyskinesia in first 5 years of treatment (%)

Age at onset of symptom (years)

40-59: N=24, 50%
60-69: N=35, 26%
70-89: N=32, 16%

Adapted from: Kumar N et al. Movement Disorders 20(3); 2005, p342-344
Proposed Etiology of Motor Fluctuations

• Advanced disease (loss of DA neurons)
• Pulsatile stimulation of dopamine receptors is necessary for the development of motor fluctuations

• Supported by experiments in rats and primates
• Supported by short-term human experiments
• No long-term human data
Initiation of Treatment

General Considerations

- Age
  - Young onset
    - motor fluctuations
    - neuroprotection
  - Older patients
    - cognitive issues
    - comorbidities

- Disability

- Cost/Compliance
Considerations in Choosing a Medical Regimen

- Side-effects of all dopaminergic agents include:
  - Nausea
  - Dyskinesias
  - Psychosis (especially in elderly)
  - Orthostatic hypotension
  - Compulsions ?

- Relative benefits of agonists are often outweighed by SE in elderly
PD Medications

- **Anticholinergic**
  - Trihexyphenidyl
    - Benztropine
  - Amantadine

- **Dopaminergic**
  - Levodopa
  - Entacapone
  - Selegiline
  - Rasagiline
  - Pramipexole
  - Ropinirole
  - Apomorphine

- **Precursor supplement**
  - L-Dopa

- **COMT inhibition**
  - Entacapone

- **MAOB inhibition**
  - Selegiline
  - Rasagiline

- **Receptor agonists**
  - Pramipexole
  - Ropinirole

- **Other**
  - Amantadine
DRUGS FOR PARKINSON’S DISEASE

Tyrosine (tyr) → l-dopa → Dopamine (DA)

- MAO-B: Selegline, Rasagiline
- COMT: Tolcapone, Entacapone
- COMT: OMD
- DOPAC
- HVA

- Amantadine
- Ropinirole
- Pramipexole
- Rotigotine
Dopamine Agonists

In early PD
- Delays need for L-dopa
- Low incidence of dyskinesia as monotherapy
- Not metabolized or effected by protein intake
- Neuroprotection ?
- Higher incidence of cognitive side-effects in the elderly and cognitively impaired
5 Yr Ropinirole vs. Levodopa

Fig. 1. Dyskinesias in MPTP monkeys. Frequency of dyskinesia in 1-methyl-4-phenyl-1,2,3,6-

Rascol 2000
268 Subjects randomized to ropinirole or levodopa

Open label supplementation allowed

HR of remaining dyskinesia free 2.82

5 yr dyskinesia: levodopa-45%; agonist-20%
82 PD patients at 17 sites in US and Canada enrolled between 1996 and 1997

Randomized to pramipexole .5mg tid or levodopa 25/100 tid

Open label levodopa could be added after 10 week escalation phase

46 month f/u

Parkinson Study Group. CALM-PD; JAMA, April 3, 2002 (287): 13
Mean percent loss in striatal Beta Cit uptake was reduced in agonist group: 7.1% vs 13.5% at 22 mos; 16% vs 25.5% at 46 mos (P=.01)

Beta Cit decline correlated with change in UPDRS (r=-.4; P=.001)
How do agonists fare after the first 4-5 years?
CALM-PD Long Term Data

Mean 6 year follow-up

158 of the 183 who completed the CALM-PD trial and 64 of the 118 who had withdrawn prematurely from the CALM-PD trial were enrolled in the CALM cohort study.
## Subject Outcomes at the Final Visit

### Table 3. Subject Outcomes at the Final Visit

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Initial Pramipexole Treatment (n=108)</th>
<th>Initial Levodopa Treatment (n=114)</th>
<th>Treatment Effect (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-reported disability by S/E ADL Scale score, mean (SD)</strong></td>
<td>79.8 (15.4)</td>
<td>81.8 (14.9)</td>
<td>2.0 (-2.1 to 6.1)</td>
<td>.34</td>
</tr>
<tr>
<td><strong>Indirect method</strong></td>
<td>79.9 (16.2)</td>
<td>82.5 (14.6)</td>
<td>2.6 (-1.4 to 7.0)</td>
<td>.19</td>
</tr>
<tr>
<td>“On” state</td>
<td>62.8 (14.9)</td>
<td>84.8 (13.6)</td>
<td>2.4 (-1.5 to 6.2)</td>
<td>.23</td>
</tr>
<tr>
<td>“Off” state</td>
<td>65.8 (21.5)</td>
<td>72.0 (17.8)</td>
<td>5.7 (-1.0 to 12.4)</td>
<td>.09</td>
</tr>
<tr>
<td><strong>Dopaminergic complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any No. (%)</td>
<td>54 (50.0)</td>
<td>78 (68.4)</td>
<td>2.46 (1.39 to 4.44)</td>
<td>.002</td>
</tr>
<tr>
<td>Dyskinesia No. (%)</td>
<td>22 (20.4)</td>
<td>42 (36.8)</td>
<td>2.56 (1.35 to 4.84)</td>
<td>.004</td>
</tr>
<tr>
<td>Wearing off No. (%)</td>
<td>48 (44.4)</td>
<td>57 (50.8)</td>
<td>2.11 (1.19 to 3.71)</td>
<td>.01</td>
</tr>
<tr>
<td>Freezing, No. (%)</td>
<td>35 (34.7)</td>
<td>26 (22.6)</td>
<td>0.72 (0.39 to 1.35)</td>
<td>.30</td>
</tr>
<tr>
<td>Lang-Fahn ADL dyskinesia scale score, mean (SD)</td>
<td>1.1 (2.9)</td>
<td>1.3 (3.2)</td>
<td>0.70 (0.0 to 1.5)</td>
<td>.06</td>
</tr>
<tr>
<td>% of waking day in “on” state, mean (SD)</td>
<td>65.6 (21.2)</td>
<td>53.9 (17.8)</td>
<td>-3.2 (-6.4 to 2.1)</td>
<td>.24</td>
</tr>
<tr>
<td><strong>UPDRS score change from baseline visit, mean (SD)</strong></td>
<td>2.4 (17.4)</td>
<td>0.5 (17.1)</td>
<td>-3.8 (-8.3 to 0.8)</td>
<td>.11</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>0.9 (2.1)</td>
<td>1.1 (2.1)</td>
<td>0.0 (-0.6 to 0.6)</td>
<td>.95</td>
</tr>
<tr>
<td><strong>ADL</strong></td>
<td>1.0 (6.2)</td>
<td>0.9 (5.2)</td>
<td>-1.3 (-2.7 to 0.1)</td>
<td>.07</td>
</tr>
<tr>
<td><strong>Nonmotor outcomes</strong></td>
<td>1.0 (12.8)</td>
<td>-1.2 (12.9)</td>
<td>-2.7 (-5.9 to 0.6)</td>
<td>.10</td>
</tr>
<tr>
<td><strong>MMSE score change from baseline visit, mean (SD)</strong></td>
<td>-1.1 (4.0)</td>
<td>-1.3 (3.9)</td>
<td>0.2 (-0.9 to 1.3)</td>
<td>.77</td>
</tr>
<tr>
<td><strong>ESS score, mean (SD)</strong></td>
<td>11.3 (5.8)</td>
<td>8.6 (4.7)</td>
<td>-2.7 (-4.0 to -1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>ESS N=70 No. (%)</strong></td>
<td>58 (57.4)</td>
<td>35 (32.6)</td>
<td>0.30 (0.22 to 0.70)</td>
<td>.002</td>
</tr>
<tr>
<td><strong>Geriatric Depression Scale score, mean (SD)</strong></td>
<td>3.3 (2.2)</td>
<td>3.1 (3.4)</td>
<td>-0.1 (-1.0 to 0.9)</td>
<td>.89</td>
</tr>
<tr>
<td><strong>Edema, No. (%)</strong></td>
<td>26 (27.1)</td>
<td>16 (14.4)</td>
<td>0.46 (0.34 to 0.59)</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Edeema that interferes with function, No. (%)</strong></td>
<td>5 (4.6)</td>
<td>5 (4.4)</td>
<td>0.36 (0.25 to 0.47)</td>
<td>.92</td>
</tr>
</tbody>
</table>

### Notes
- **PDQULIT**: Parkinson Disease Quality-of-Life Scale
- **SIE** Schwab and England
- **SF-12**: 12-Item Short Form Health Survey
- **UPDRS**: Unified Parkinson’s Disease Rating Scale
- **VAS**: visual analog scale

**Abbreviations:**
- ADL: activities of daily living
- CI: confidence interval
- ESS: Eschworth Sleepiness Scale
- MMSE: Mini-Mental State Examination
- PDQULIT: Parkinson Disease Quality-of-Life Scale
- SIE: Schwab and England
- SF-12: 12-Item Short Form Health Survey
- UPDRS: Unified Parkinson’s Disease Rating Scale
- VAS: visual analog scale

For continuous outcomes, the treatment effect is expressed as the group difference in adjusted mean response (levodopa minus pramipexole) derived from an analysis of covariance model. For dichotomous outcomes, the treatment effect is expressed as the adjusted odds ratio (levodopa to pramipexole) derived from a logistic regression model. See text for details.

Review of Rochester Epidemiology Project medical records linkage system

All incident PD patients treated with levodopa in Olmstead county 1976-1990

126 patients

Based on KM analysis, estimated dyskinesia rate: 30% at 5 treatment years, 59% by 10 years

Bothersome dyskinesia: 17% at 5 yrs, 43% at 10 yrs

Troublesome dyskinesia 12% at 10 yrs

Univariate analysis: older age by 10 yrs decreased risk: HR .72

Prevalence of motor complications at 10 years

Table 2  Prevalence of motor complications at final follow-up

<table>
<thead>
<tr>
<th>Prevalence at final follow-up</th>
<th>L-dopa arm (n = 42)</th>
<th>Bromocriptine arm (n = 63)</th>
<th>Difference* (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any dyskinesia</td>
<td>58%</td>
<td>56%</td>
<td>−5.3% (−25%, 15%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Moderate/severe dyskinesia</td>
<td>39%</td>
<td>35%</td>
<td>−6.0% (−25%, 13%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Any fluctuations</td>
<td>50%</td>
<td>56%</td>
<td>5.1% (−15%, 25%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Moderate/severe fluctuations</td>
<td>33%</td>
<td>35%</td>
<td>0.01% (−19%, 19%)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*Adjusted for baseline characteristics (age, duration of disease, baseline Hoehn & Yahr, Northwestern University Disability, and Webster ratings).

- PDRG-UK trial comparing levodopa, l-dopa + selegiline, and bromocriptine
- 782 subjects 1985-1990 randomized; 166 available at final assessment (21%)
- Mean duration follow-up at final assessment 14 yrs
- Disability scores were better in l-dopa arm after adjustment for baseline characteristics (p=.03)
- No difference in mortality rates, prevalence of dyskinesia, and dementia
Dopamine Agonists: Distinguishing Features

- Directly stimulate dopamine receptors
- No metabolic conversion; bypasses nigrostriatal neurons
- No absorption delay from competition with dietary amino acids
- Longer half-life than levodopa
- Monotherapy or adjunct therapy
- May delay or reduce motor fluctuations & dyskinesias associated with levodopa
- May be neuroprotective
DAs: Common Adverse Effects

- Nausea, vomiting
- Dizziness, postural hypotension
- Headache
- Dizziness
- Drowsiness & somnolence
- Dyskinesias
- Confusion, hallucinations, paranoia
- ???ICDs
Selegiline

- Irreversible MAO-B inhibitor
- Clinically active by inhibiting dopamine metabolism in brain
- May be neuroprotective
- Dosage: 5 mg at breakfast and lunch
- Side effects: insomnia, hallucinations, nausea (rarely), OH
- Potential interactions with tricyclics and SSRI antidepressants
Rasagiline: The TEMPO Trial

Rasagiline -
the ADAGIO trial

### Table 2. Results for the Primary and Secondary End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Estimated No. of Points</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First primary (estimated rate of change in UPDRS score/wk, wk 12–36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.14±0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasagiline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day</td>
<td>0.09±0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/day</td>
<td>0.07±0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day vs. placebo</td>
<td>-0.05±0.02</td>
<td>-0.08 to -0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>2 mg/day vs. placebo</td>
<td>-0.07±0.02</td>
<td>-0.11 to -0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second primary (estimated change in total UPDRS score from baseline to wk 72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasagiline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day, early start</td>
<td>2.82±0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day, delayed start</td>
<td>4.50±0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/day, early start</td>
<td>3.47±0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/day, delayed start</td>
<td>3.11±0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day, early start vs. delayed start</td>
<td>-1.68±0.75</td>
<td>-3.15 to -0.21</td>
<td>0.02</td>
</tr>
<tr>
<td>2 mg/day, early start vs. delayed start</td>
<td>0.36±0.68</td>
<td>-0.99 to 1.70</td>
<td>0.60</td>
</tr>
<tr>
<td>Third primary (estimated rate of change in UPDRS score/wk, wk 48–72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasagiline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day, early start</td>
<td>0.08±0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day, delayed start</td>
<td>0.08±0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/day, early start</td>
<td>0.09±0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/day, delayed start</td>
<td>0.06±0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day, early start vs. delayed start</td>
<td>0.00±0.02</td>
<td>-0.04 to 0.04‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 mg/day, early start vs. delayed start</td>
<td>0.03±0.02</td>
<td>-0.01 to 0.06‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary (change in total UPDRS score from baseline to final visit in phase 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>4.27±0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasagiline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day</td>
<td>1.26±0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/day</td>
<td>1.11±0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg/day vs. placebo</td>
<td>-0.01±0.43</td>
<td>-3.86 to -2.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 mg/day vs. placebo</td>
<td>-3.15±0.43</td>
<td>-4.00 to -2.31</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Rasagiline

The Adagio Trial

Levodopa

- Most effective drug for parkinsonian symptoms
- First developed in the late 1960s; rapidly became the drug of choice for PD
- Large neutral amino acid; requires active transport across the gut-blood and blood-brain barriers
- Rapid peripheral decarboxylation to dopamine without a decarboxylase inhibitor (DCIs: carbidopa, benserazide)
- Side effects: nausea, postural hypotension, dyskinesias, motor fluctuations
Sinemet

L-dopa
- Most effective Rx for majority of Sx
- Pulsatile use likely leads to motor fluctuations
- Carbidopa >75 mg/day
Is Levodopa Toxic?

- Early patients develop motor fluctuations, but may be a function of neuronal cell loss
- Increased life expectancy with LD introduction
- LD-naive advanced PD patients develop fluctuations almost immediately with LD induction
- No LD neuronal dropout in laboratory animals
- Some believe continuous infusion may be safer than pulsatile therapy
Levodopa Toxicity: The ELLDOPA Trial

Fahn S and The Parkinson’s Study Group N Engl J Med
351;24 December 9 2004
Levodopa-Induced Dyskinesias

- Manifestation of excessive dopaminergic stimulation
- Typically late effect, and with higher doses
- Narrowing of therapeutic window
- Rare in LD-naive patients on DA monotherapy
- Most common is "peak dose" dyskinesia
  - disappears with dose reduction
- Choreiform, ballistic and dystonic movements
- Most patients prefer some dyskinesias over the alternative of akinesia and rigidity
# Levodopa/Carbidopa Formulations

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Release</td>
<td>20-40 min</td>
<td>2-4 hr</td>
</tr>
<tr>
<td>10/100, 25/100, 25/250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled Release</td>
<td>30-60 min</td>
<td>3-6 hr</td>
</tr>
<tr>
<td>25/100, 50/200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODT</td>
<td>dissolves on contact with saliva but no transmucosal absorption</td>
<td></td>
</tr>
</tbody>
</table>
Pulsatile vs. Tonic DA Receptor Stimulation
Principles of Managing Fluctuations

- Decrease fluctuations of L-dopa blood levels
  - Use smaller more frequent dosing.
  - Use combination of regular Sinemet and Sinemet CR.
  - Add COMT inhibitor
  - Add MAO-B inhibitor

- Add amantadine

- Surgery
COMT Inhibition

- Increases the half-life of L-dopa plasma concentrations without affecting peak values thus reducing fluctuations in L-dopa concentrations
- Decreases concentration of O-methyl-dopa which may reduce competition for the NAA transporter.
EFFECT OF COMT-I ON PLASMA L-DOPA LEVELS

L-DOPA

time

Sinemet

with COMT-I

without COMT-I
COMT Inhibitors

- Newest class of antiparkinsonian drugs: tolcapone (use best restricted to PD specialist), entacapone
- MOA similar to dopa decarboxylase inhibitors
- Potentiate LD: prevent peripheral degradation by inhibiting catechol O-methyl transferase
- Reduces LD dose necessary for a given clinical effect
- Helpful for both early and fluctuating Parkinson’s disease
- May be particularly useful for patients with “brittle” PD, who fluctuate between off and on states frequently throughout the day
Entacapone

- Dosage: 200 mg w/each levodopa dose
- Parkinson’s Study Group 1997: Increased on time by 5%, more in pts w/least on time
- Rinne et al., 1998: Increased on time by ~10%; decreased levodopa
- Diarrhea, dopaminergic SEs
Amantadine

Antiviral agent; PD benefit found accidentally

Tremor, bradykinesia, rigidity & dyskiniesias

Exact mechanism unknown; possibly:
- enhancing release of stored dopamine
- inhibiting presynaptic reuptake of catecholamines
- dopamine receptor agonism
- NMDA receptor blockade

Side effects — autonomic, psychiatric

200-300 mg/day
Anticholinergics

- Dopaminergic depletion → cholinergic overactivity
- Initially used in the 1950s
- Effective mainly for tremor and rigidity
- Common agents (Start low, go slow):
  - Trihexyphenidyl: 2-15 mg/day
  - Benztropine: 1-8 mg/day
  - Ethopropazine: 10-200 mg/day
- Side effects:
  - Dry mouth, sedation, delirium, confusion, hallucinations, constipation, urinary retention
Apomorphine

- D1/D2 agonist
- Parenteral delivery (s.c., i.v., sublingual, intranasal, rectal)
- Rapid “off” period rescue
  - 2-5 mg s.c.; pen injection systems
- Treatment of unpredictable, frequent motor fluctuations
  - continuous s.c. infusion via mini-pump
- SE: nausea, vomiting, hypotension
  - trimethobenzamide 250 mg t.i.d.
  - domperidone 20 mg t.i.d.; not available in U.S.
Considerations in Choosing a Medical Regimen

- Sinemet is the most effective medication
- L-Dopa probably doesn’t kill cells and works for more than 5 yrs.
- L-Dopa primes system for motor fluctuations (pulsatile vs tonic use)
- Agonists delay onset of motor fluctuations
- All PD medications have more side-effects in elderly
Co-Enzyme Q10

• Complex I deficiency in PD
• Co-Q10 is a cofactor for Complex I
• Co-Q10 restores activity in vitro

16 Month Study

Change in tUPDRS

Placebo
300 mg
600 mg
1200* mg

Shults et al. 2002
Considerations in Choosing a Medical Regimen

- Potency
- Side-effects
  - Nausea
  - Psychosis (especially in elderly)
  - Orthostatic hypotension
  - Peripheral edema
  - Compulsions?

Relative benefits of agonists are often outweighed by SE in elderly
Problems in Advanced Parkinson’s Disease

- Motor fluctuations (young onset > older).
- Falls
- Medication-induced psychosis
- Depression
- Sleep
- Cognitive decline
Initiating Therapy

Disabled

Yes
- MAO-B I
- agonist (young)
- Sinemet

No
- educate
- exercise
- MAO-B I?
- agonist?

AE Risk?