Philadelphia VA PADRECC

Parkinson's Disease Research, Education & Clinical Center

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

Restorative Therapies
cells, genes, trophic factors

LIMIT COGNITIVE AND NON-DOPAMINERGIC SYMPTOMS

Dementia
Depression
Postural Instability
Freezing
Autonomic failure

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**

Table 6. Comparison of Age and Duration of Illness at Death between Pre- and Post-levodopa Series of Patients

	Number of Patients	Number of Deaths	Age at Death, *yrs.*		Duration of Illness	
			Mean	Range	Mean	Range
Pre-levodopa (13)	802	340	65.9	38-91	10.8	1-41
Post-levodopa (present series)	100	32	73.1	63-90	12.1	3-28

Sweet et al., Ann Int Med 1975:83;456-463

Neuroprotective Trials in PD

Class	Trial	N[a]	Primary outcome	Duration
Antiapoptotic agents				
–TCH346	Olanow et al. [42]	301	Time to symptomatic treatment	12–18 months
–CEP-1347	PRECEPT [45]	806	Time to symptomatic treatment	Terminated after ~21 months
–Minocycline	NINDS NET-PD FS-1 [47]	200	Change in total UPDRS	12 months
Antioxidants				
–Vitamin E	DATATOP [73]	800	Time to symptomatic treatment	Terminated after ~12 months
–Coenzyme Q10	QE2 [5]	80	Change in total UPDRS	16 months
	NINDS NET-PD FS-Too [62]	213	Change in total UPDRS	12 months
–Creatine	Bender et al. [72]	60	^{123}I-β-CIT SPECT changes	24 months
	NINDS NET-PD FS-1 [47]	200	Change in total UPDRS	12 months
Dopamine agonists				
–Pramipexole	CALM-PD [21,31]	82	^{123}I-β-CIT SPECT changes	46 months
–Ropinirole	REAL-PET [32]	186	^{18}F-DOPA PET changes	24 months
–α-dihydroergocryptine	Pöpperl et al. [79]	25	^{123}I-IPT SPECT changes	52 weeks
Glutamate antagonists				
–Riluzole	Jankovic and Hunter [88]	20	Change in UPDRS II and III	6 months
	Rascol et al. [89]	1084	Time to symptomatic treatment	Prematurely terminated
Levodopa				
–Levodopa	ELLDOPA [24]	361	Change in total UPDRS	40 weeks
MAO inhibitors				
–Selegiline	DATATOP [73]	800	Time to symptomatic treatment	Terminated after ~12 months
	Tetrud and Langston [99]	54	Time to symptomatic treatment	3 years
	SINDEPAR [102]	101	Change in total UPDRS	14 months
	Swedish Parkinson Study Group [100]	157	Time to symptomatic treatment	1–3 years
	Norwegian–Danish Study Group [103]	79	Change in total UPDRS	60 months
–Lazabemide	ROADS [4]	321	Time to symptomatic treatment	12 months
–Rasagiline	TEMPO [7]	404	Change in total UPDRS	12 months
Neuroimmunophilin ligands				
–GPI-1485	NIL-A phase II clinical trial [111]	300	Change in UPDRS motor score	6 months
	NINDS NET-PD FS-Too [62]	213	Change in total UPDRS	12 months
Neurotrophic factors				
–GDNF	ICV GDNF Study Group [117]	50	Change in UPDRS motor score	8 months
	Lang et al. [119]	34	Change in UPDRS motor score	6 months

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

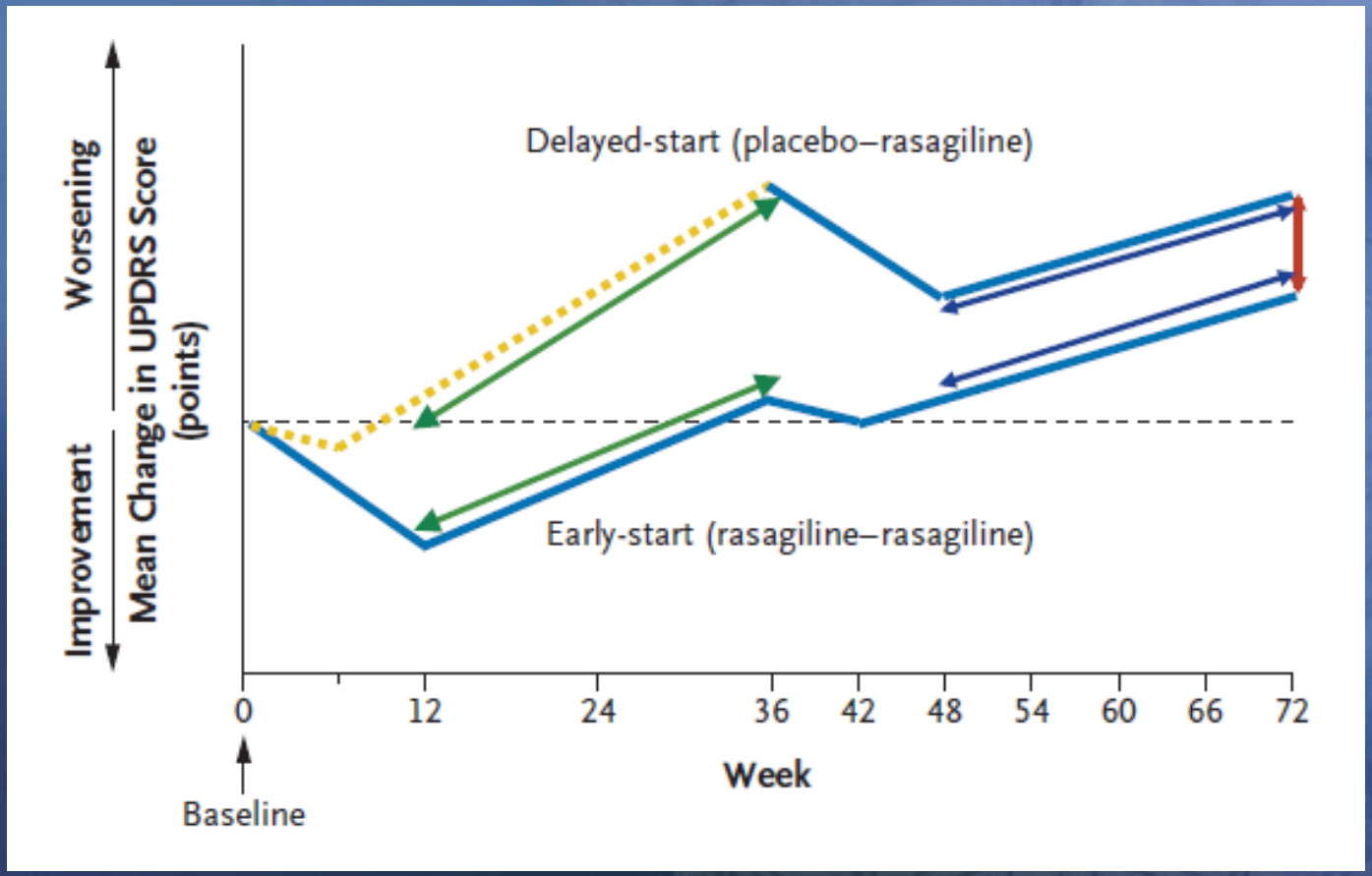
- Mouse substantia is not nigra – not pigmented
- Presumably equal expression of α-synuclein does not lead to aggregation/ neuronal demise in mice as it does in humans
- Mouse lifespan much shorter – most studies ignore the seemingly essential effects of aging
- A53T α-synuclein mutation in humans is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

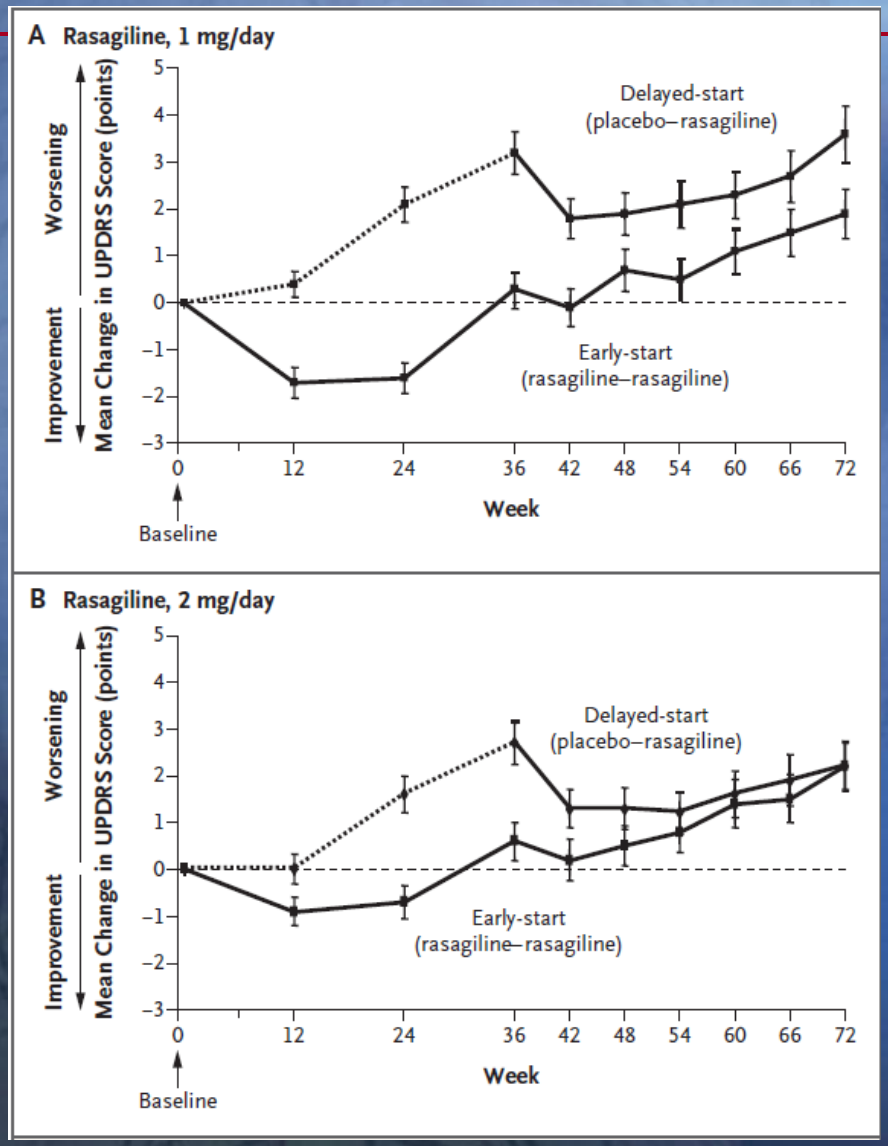
ADAGIO Endpoints



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

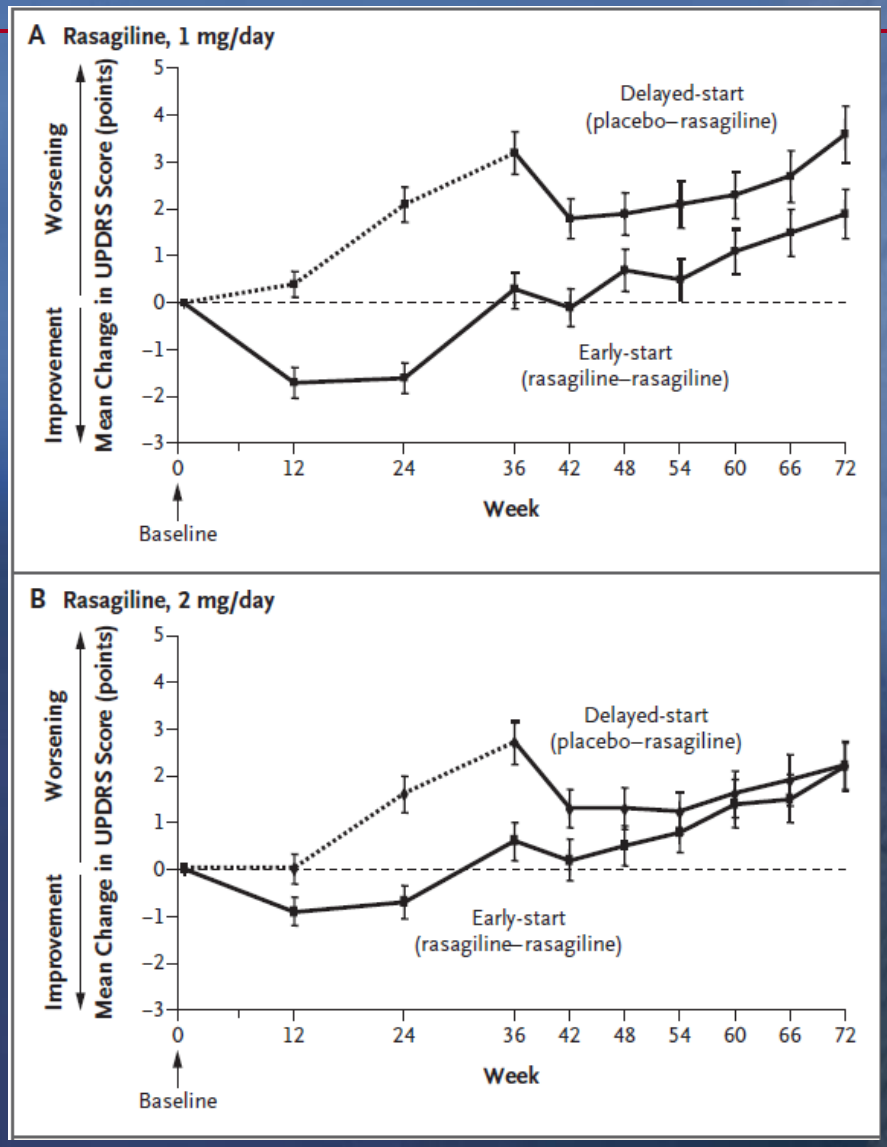
Other Problems

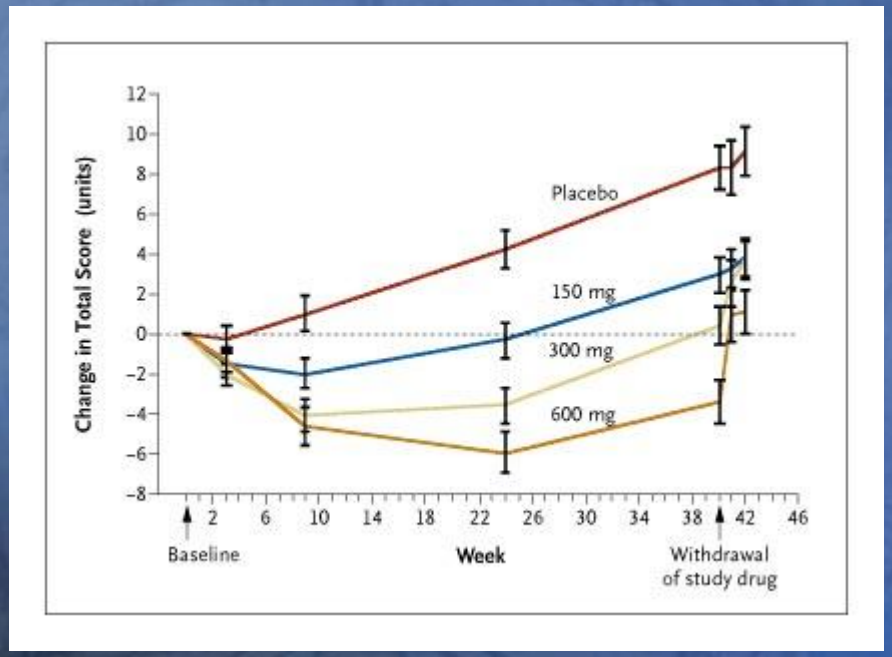
- Variability in response to rasagiline was twice the magnitude of the positive finding of the study:
  - Delayed-start, active phase 2mg +1.16 pts
  - Delayed-start, active phase 1mg -0.23
  - Early-start, first phase 2mg -1.11
  - Early-start, first phase 1mg -1.26
  - Early-start, second phase 1mg -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 rasagiline even do better than levodopa?

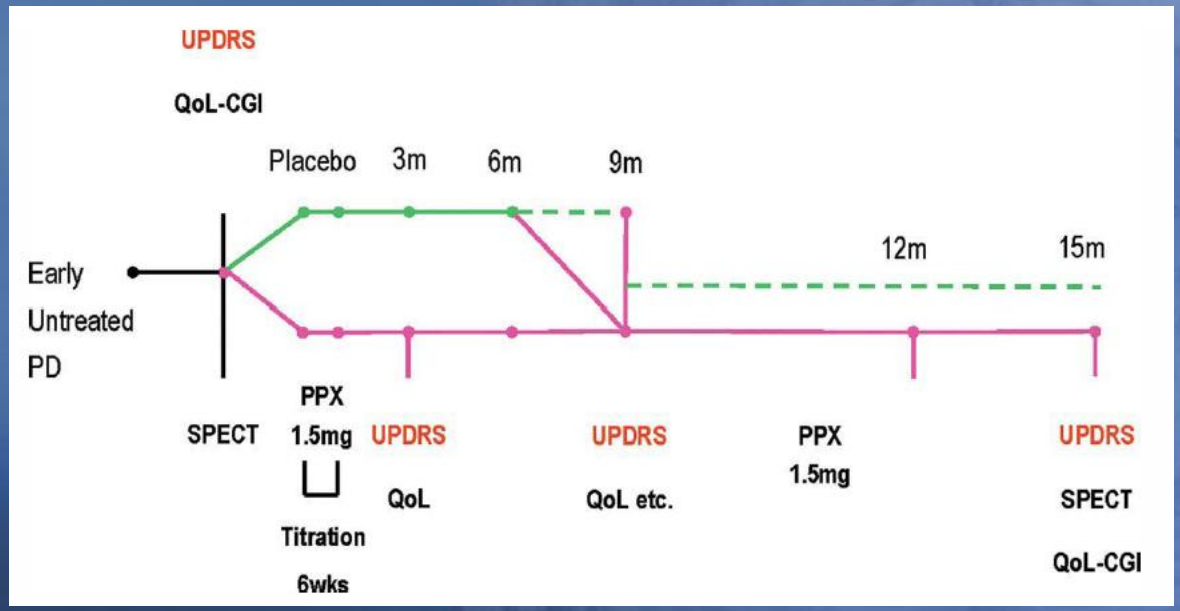
Adagio vs. Elldopa





Fahn et al. NEJM 2004;351: 2498-508

The PROUD Study
Pramipexole on Underlying Disease

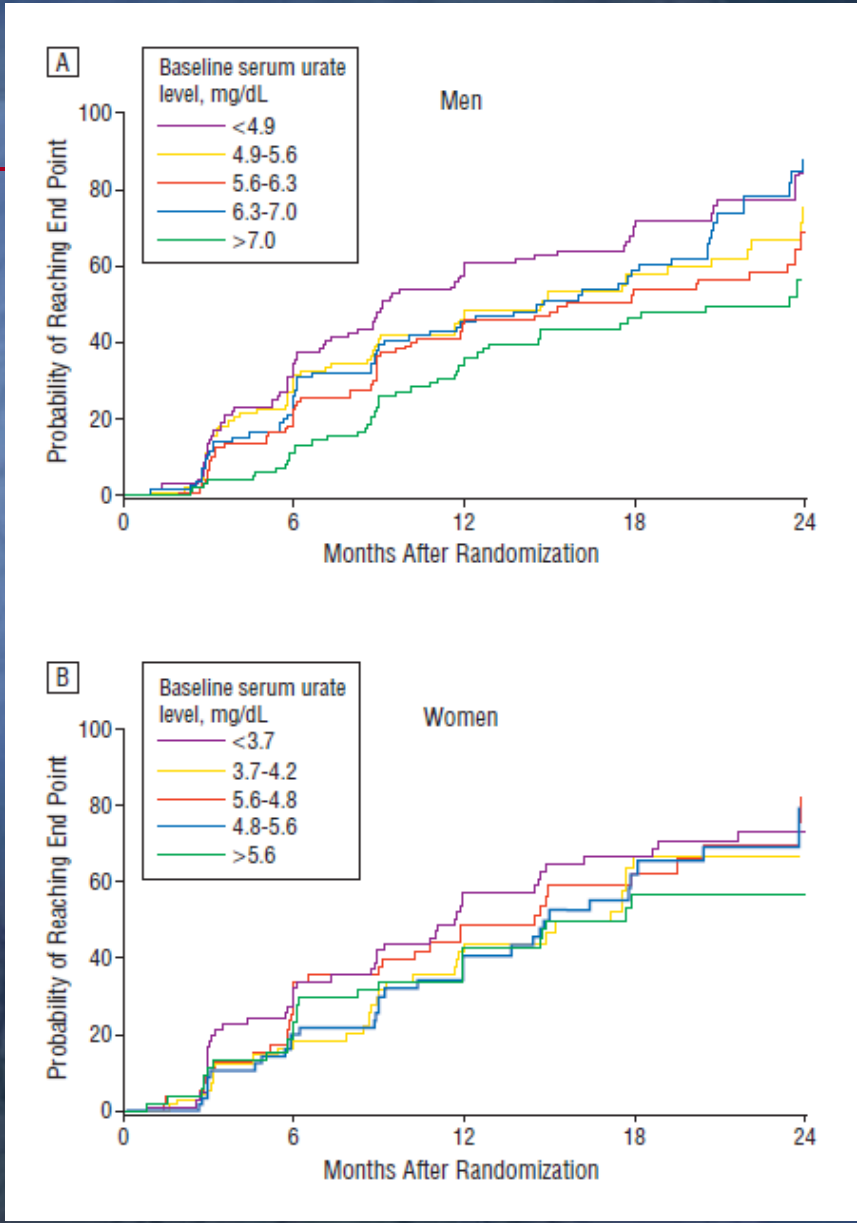


- 535 de novo PD patients – 411 in primary comparison
- Primary outcome was change from baseline in total UPDRS
  - No difference between pramipexole and placebo
- Secondary outcomes:
  - PDQ39 – not significantly different
  - DATSCAN – not significantly different

Schapira et al. Parkinsonism Relat Disord 2009;15:S2–S81.

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?

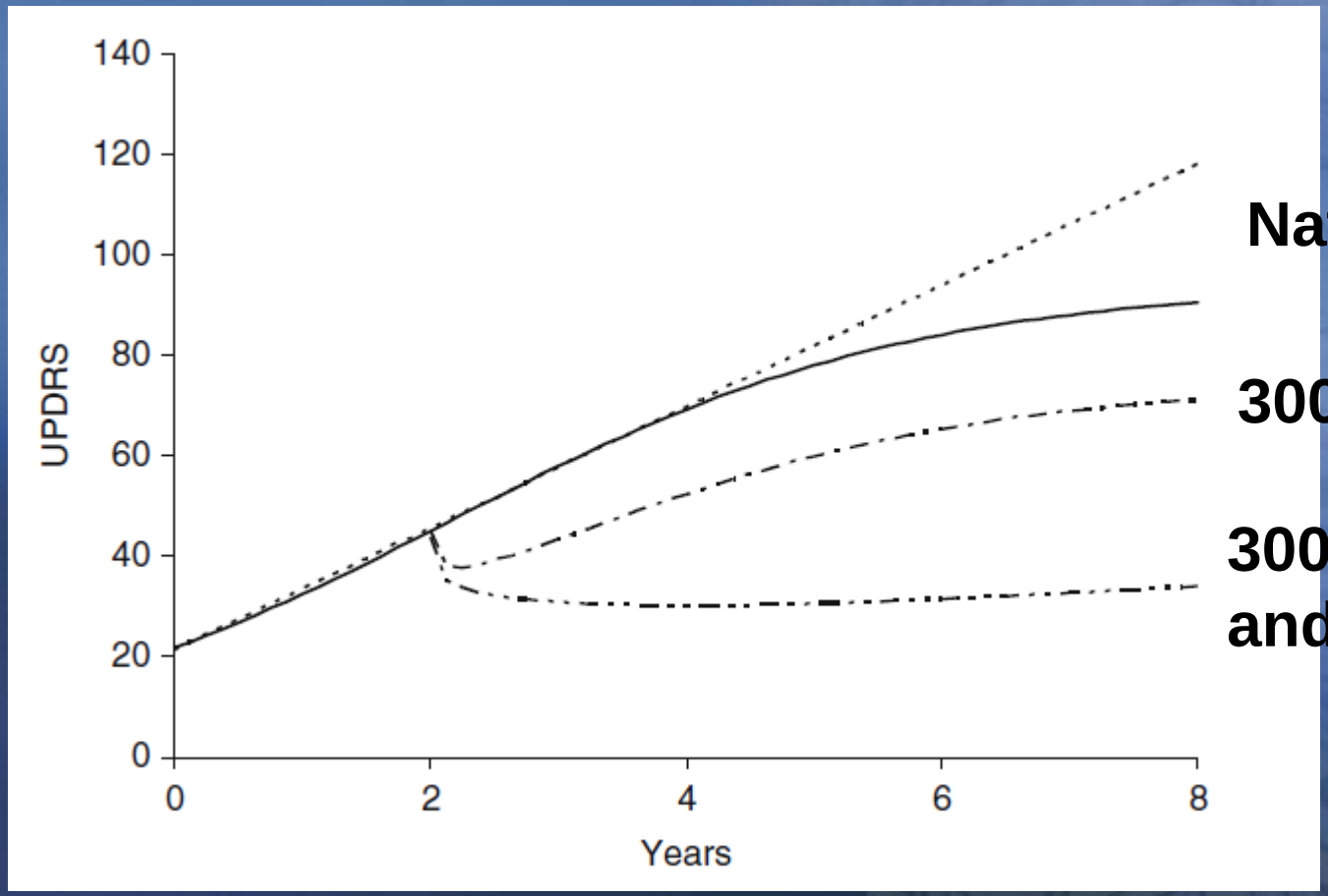
- Recognize the limitations of relying on models utilizing acute toxic injuries
- Reconsider delayed start trial design
- Consider novel ways to model outcomes
- Replace UPDRS with quantitative assessments

Potential neuroprotective drugs	
Ascorbic acid	GM-1 ganglioside[a]
Amantadine	Minocycline[a]
Azulenyl nitrone	Modafinil
Caffeine[a]	N-acetylcysteine
Coenzyme Q10[a]	Nicotine
COX I-II inhibitors	Pramipexole[a]
Creatine[a]	Ropinirole[a]
Erythropoietin	Rasagiline[a]
Estrogen[a]	Remacemide
Folate	Selegiline[a]
GPI-1485[a]	GM-1 ganglioside[a]

[a] Candidates for near-term Phase II or III neuroprotection studies.

Ravina et al. Neurology 2003;60:1234–40.

Re-analysis of DATATOP data



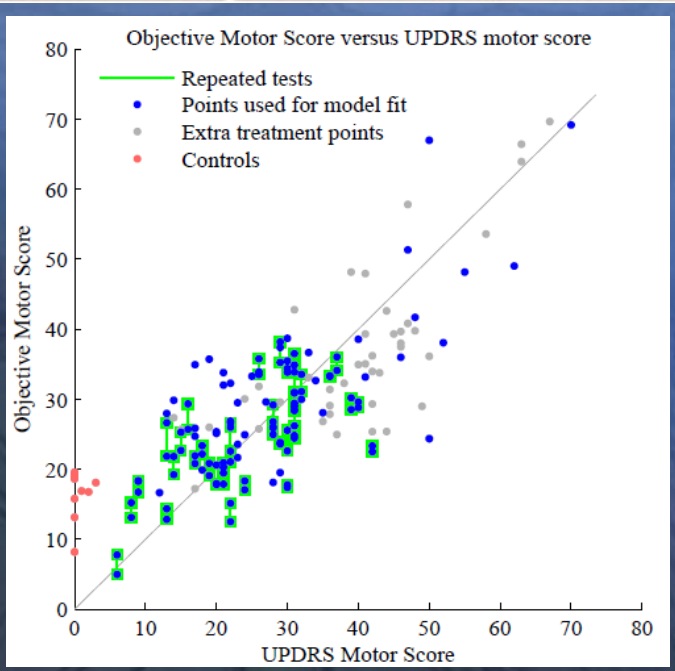
Natural history

300mg levodopa

300mg levodopa and selegiline

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

Quantitative Motor Assessments



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