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

$$E = E0 + \frac{E\max \cdot Conc}{EC50 + Conc}$$

Disease Progress

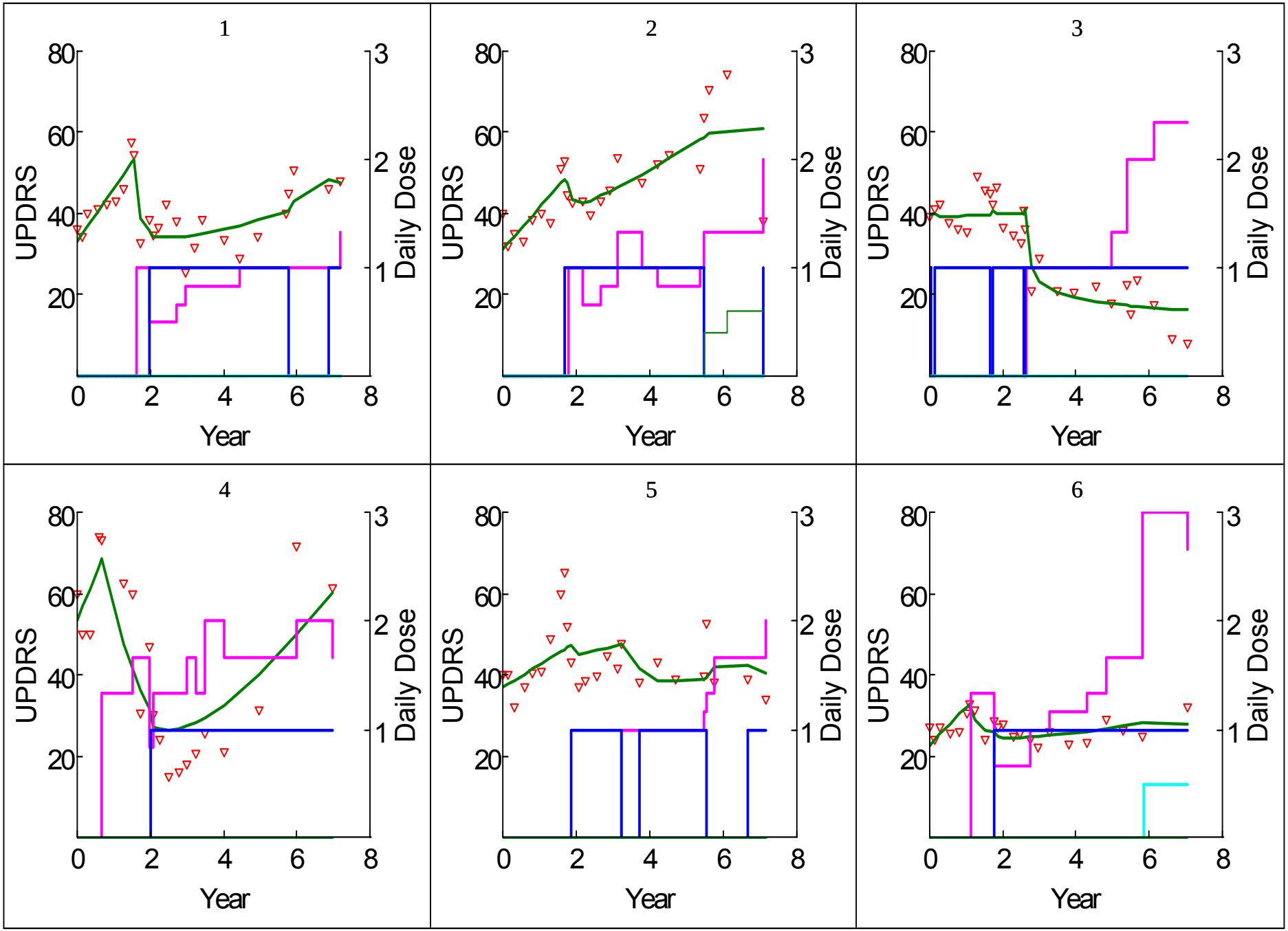
Drug Action

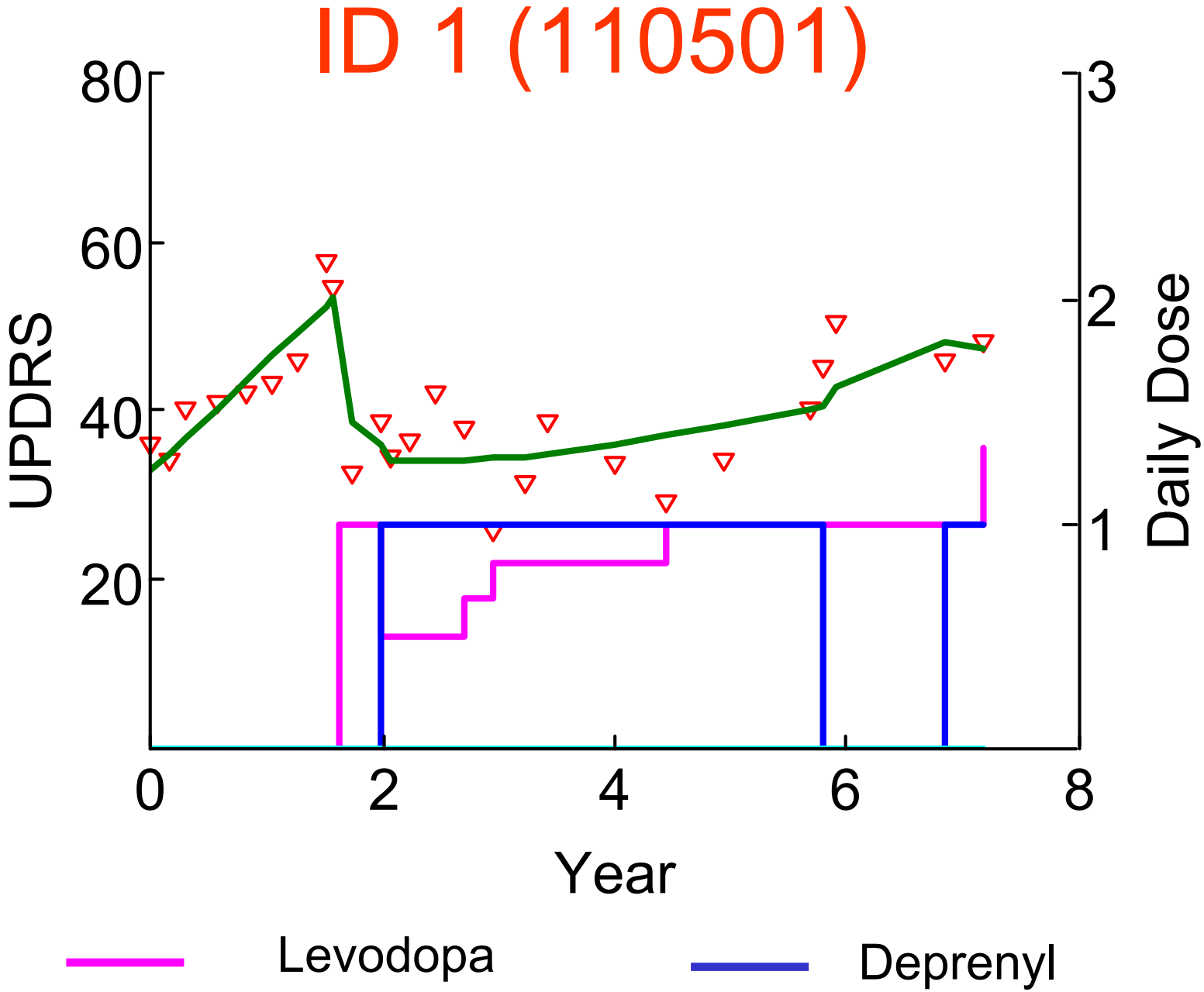
Parkinson Study Group
DATATOP Cohort

Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism

PKPD of anti-parkinsonian treatment
and Parkinson's disease over 7 years
in 800 patients

The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. The New England Journal of Medicine 1989;321:1364-1371





Drug Action Symptomatic

$$E(t) = \frac{E\max(t) \bullet Ce_{LD}(t)}{ED50 + Ce_{LD}(t)}$$

$$E\max(t) = E\max_0 + BEML \bullet \left(1 - \exp\left(\frac{\ln(2)}{TEML} \bullet t\right)\right)$$

CeLD(t)	= Effect compartment LD ‘concentration’
E(t)	= Effect at daily levodopa dose LD
$Emax_0$	= Baseline Max symptomatic effect of levodopa
ED50	= LD producing 50% of Emax(t)
BEML	= Emax change at steady state
TEML	= Half-life of Emax change time

Disease Progress and Drug Action

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

Exponential $$\frac{dS}{dt} = \frac{\ln(2)}{Tprog} \cdot (Sss \cdot f(Rx) - S)$$

Gompertz $$\frac{dS}{dt} = \frac{\ln(2)}{Tprog \cdot f(Rx)} \cdot (Sss - S) \cdot S$$

α = Linear progression rate
Tprog = Progression ‘half-life’
Sss = Asymptotic ‘burnt out’ steady state

Protective Drug Action & Interaction

Levodopa $$FPLD = \exp(KPL \bullet C_{LD}(t))$$

Deprenyl $$FPDP = \exp(KPD \bullet C_{DP}(t))$$

$$\theta(LD, DP) = \theta_0 \bullet FLXD \bullet FPLD \bullet FPDP$$

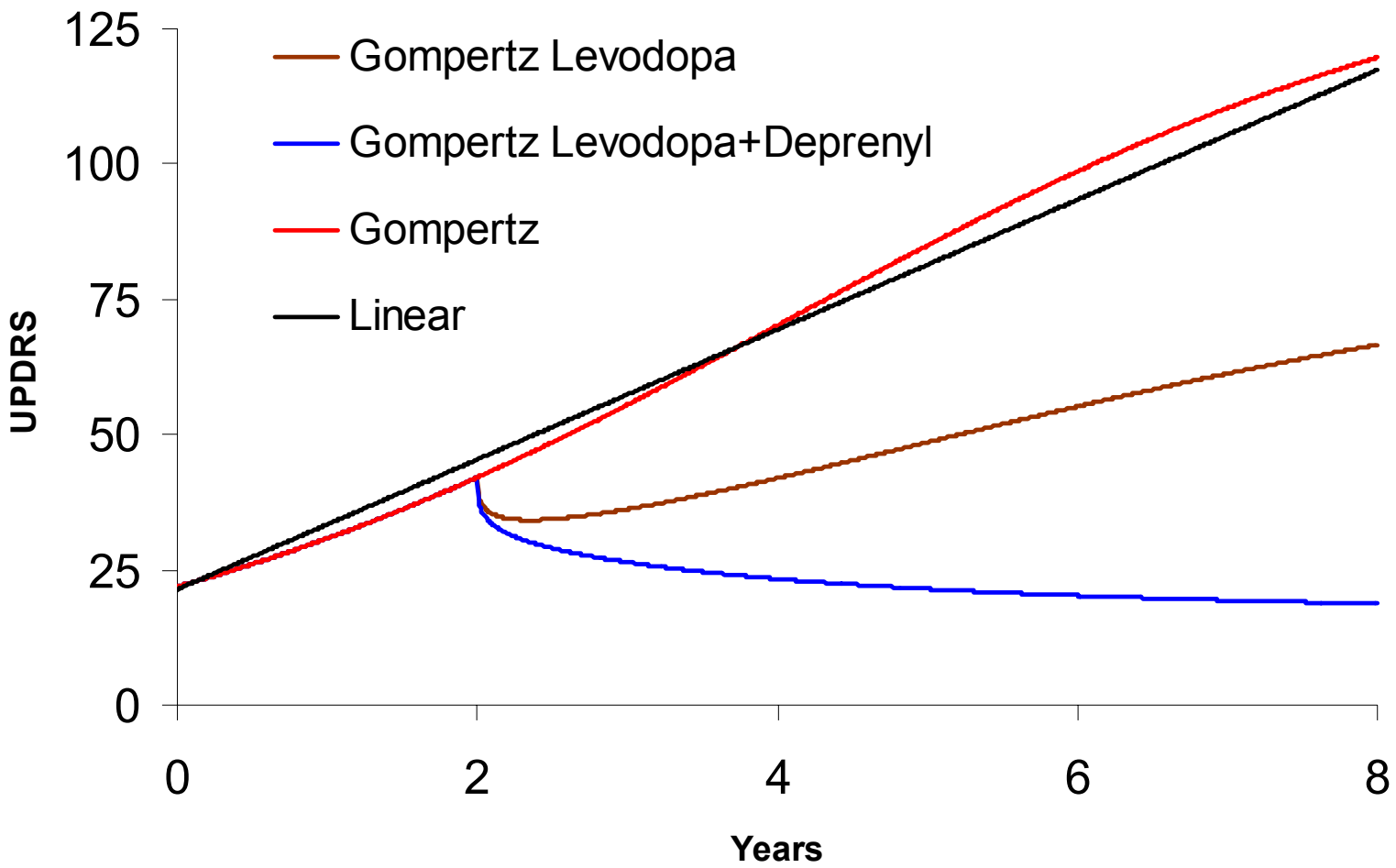
$C_{LD}(t)$ = Css levodopa at time t
KPL = Levodopa protective parameter
$C_{DP}(t)$ = Css deprenyl at time t
KPD = Deprenyl protective parameter
FLXD = Levodopa * Deprenyl interaction
θ_0 = Untreated progression parameter

Disease Progress Models

Progress Model	Obj	SigDig	S0 U	α U/Year	Sss U	Tprog Years
Gompertz Tprog	76306	3.7	21.8	.	94	117
Gompertz Sss	76366	3	21.9	.	140	227
Linear Alpha	76638	5.9	21.4	12.1	.	.

Best model is Gompertz with Drug Action on Tprog

Gompertz Disease Progress

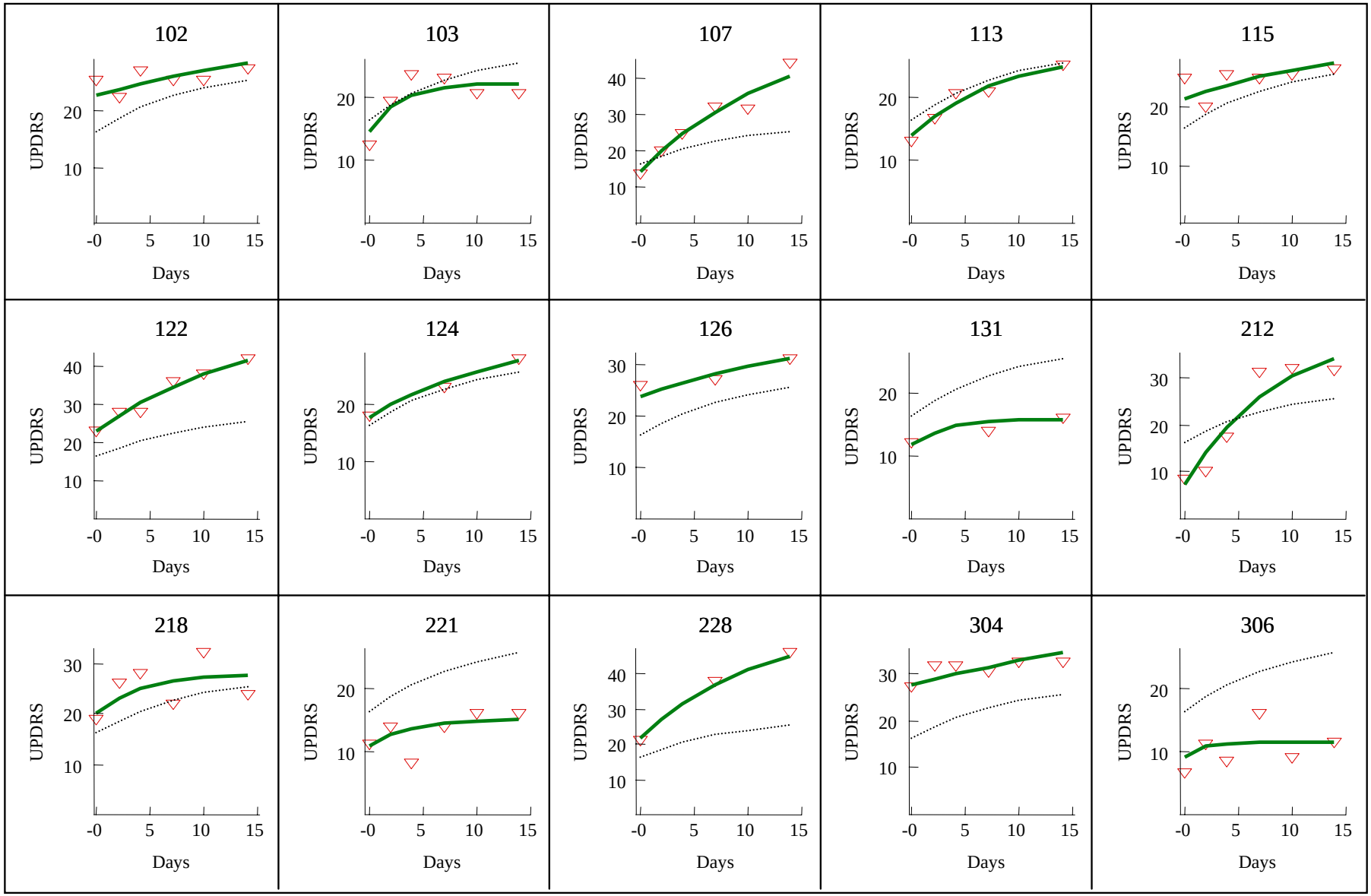


Wash-Out Study
Hauser et al.

- 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

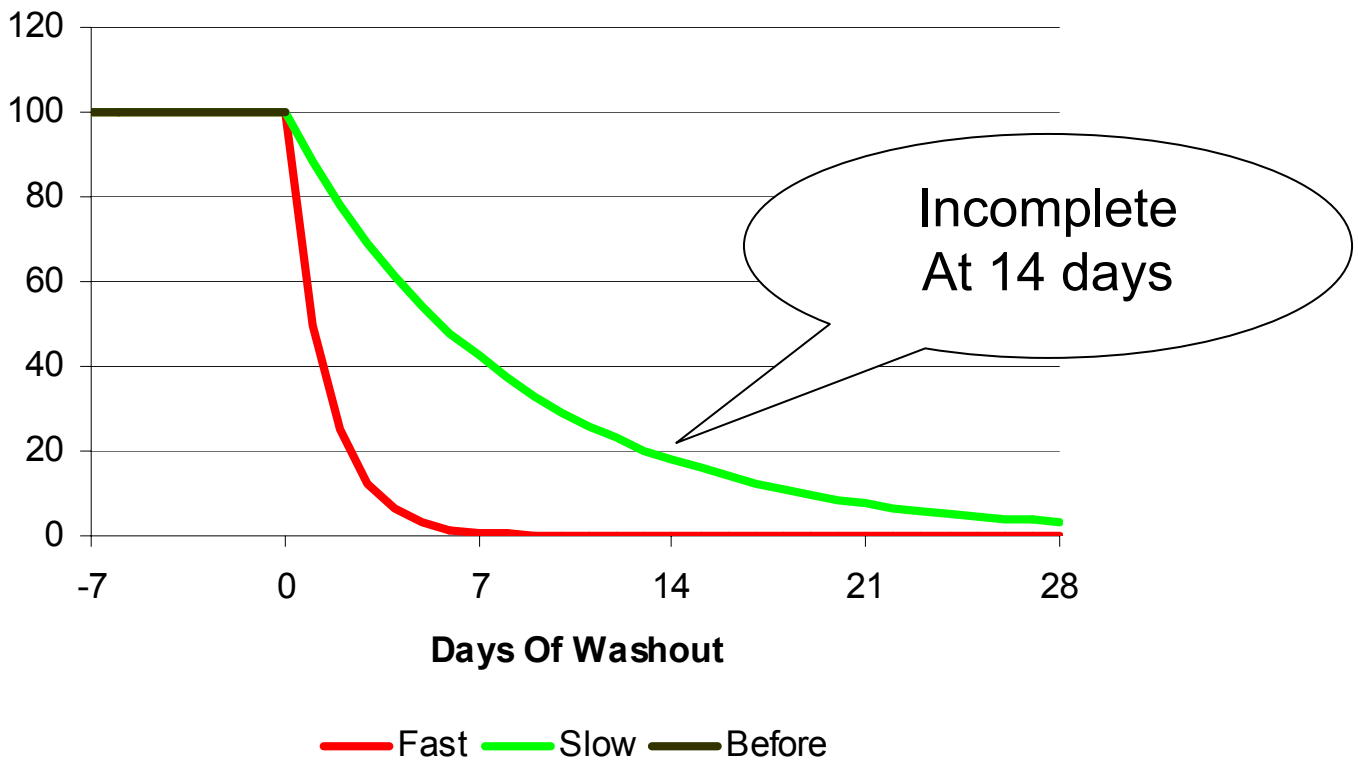
Hauser RA, Holford NHG. Quantitative description of loss of clinical benefit following withdrawal of levodopa-carbidopa and bromocriptine in early Parkinson's disease. Movement Disorders 2002;17(5):961-8

Levodopa Washout



Washout Predictions

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



ELLDOPA Study

ELLDOPA – Earlier vs Later L-DOPA

Control

- Placebo

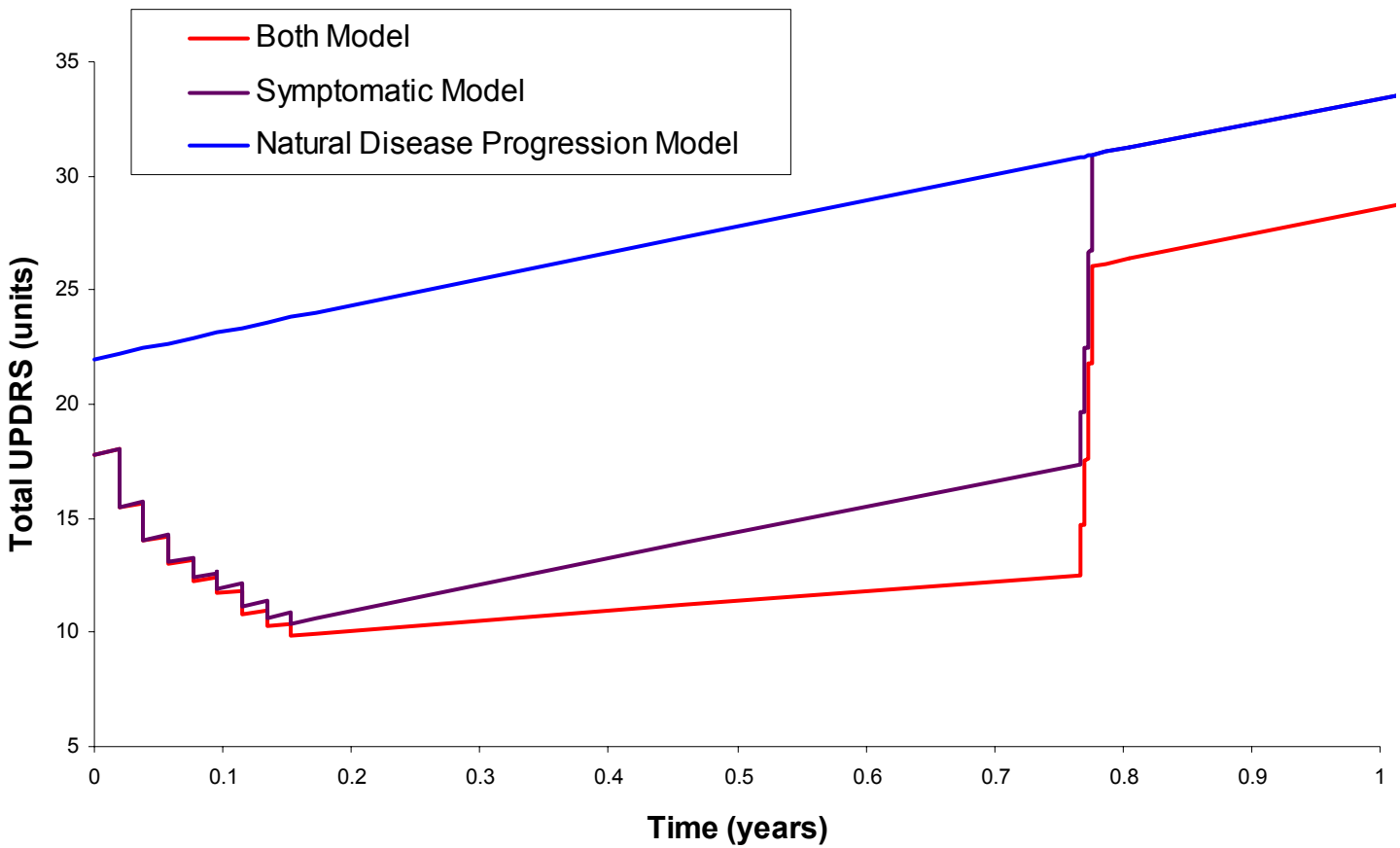
Levodopa

- 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

Predicted ELLDOPA Effects



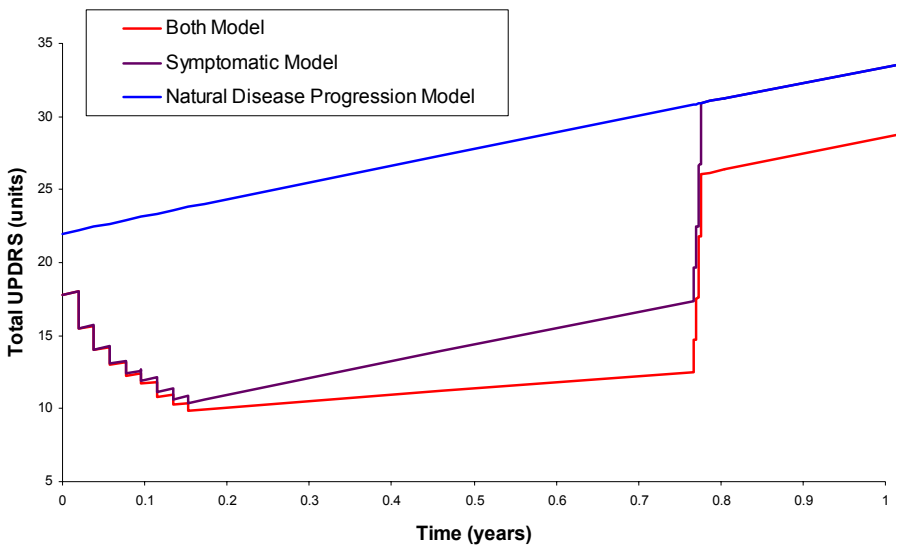
ELLDOPA assumes all symptomatic effect is washed out at 2 weeks

ELLDOPA Power

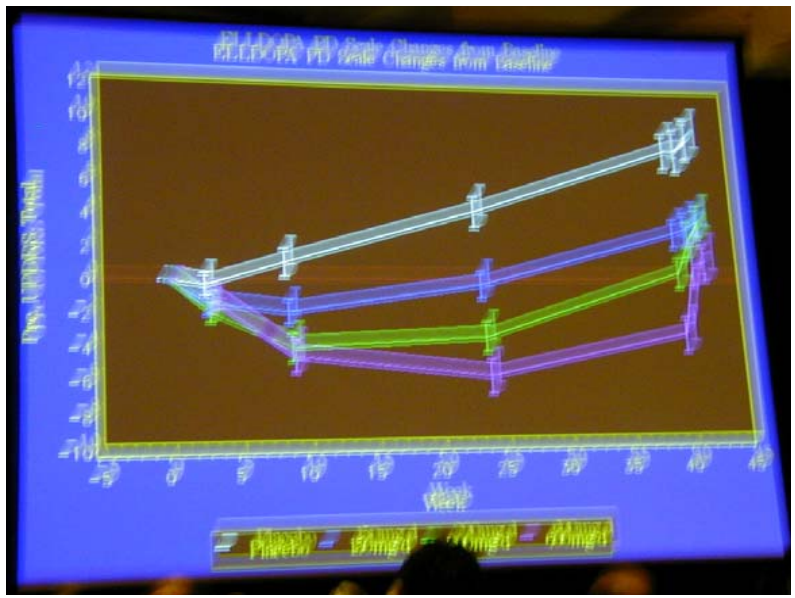
Null Hypothesis LD=Placebo α=0.05

Drug Action	Washout of symptomatic benefit	Power (%) ± SE
Symptomatic	Fast	7 ± 3
	Slow	100 ± 0
Symptomatic + Protective	Fast	86 ± 3
	Slow	100 ± 0

Does Levodopa Affect Parkinson's Progression?



Design - Clear



Results - Murky

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

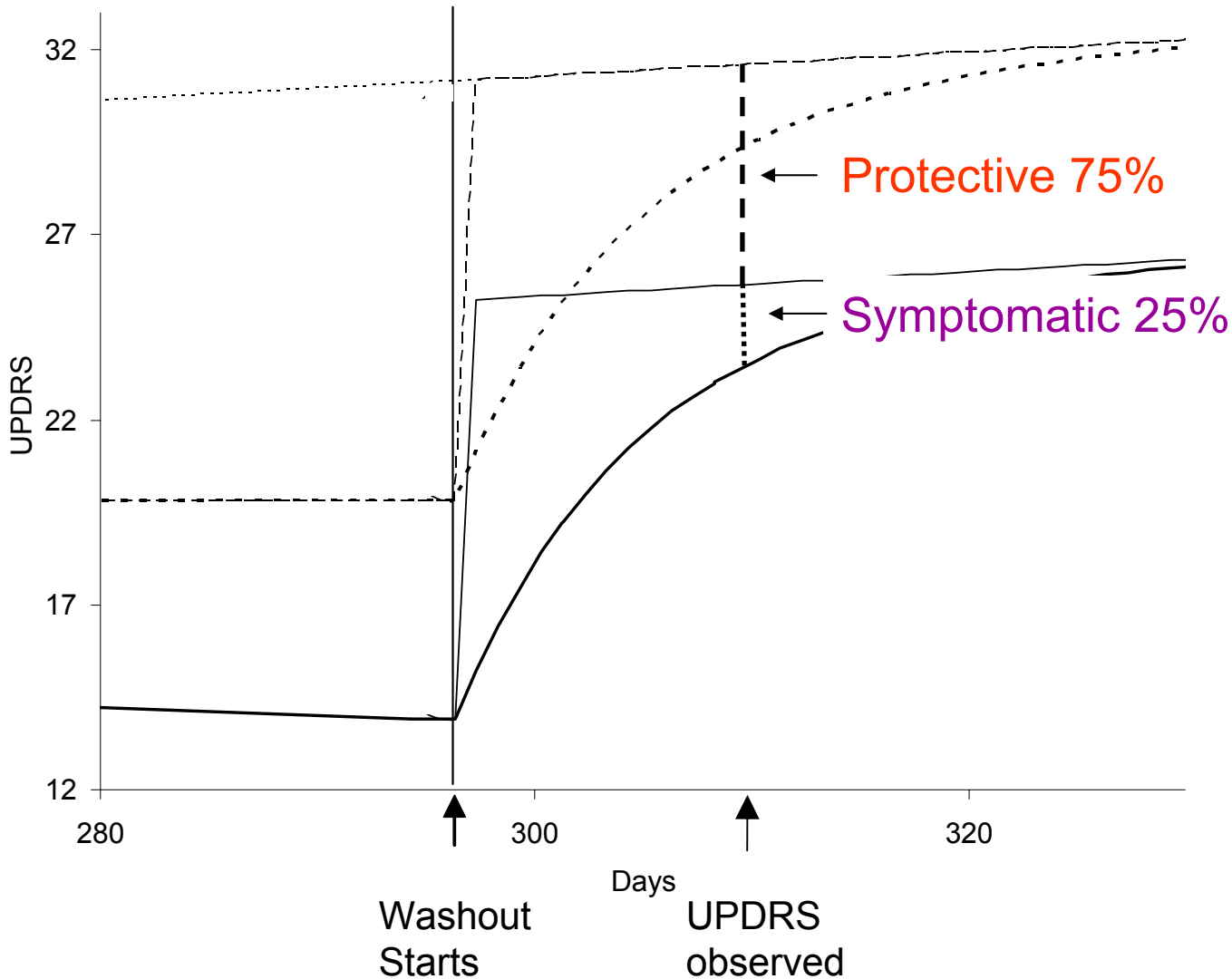
Predicted & Observed

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

Levodopa Protective	Low 150 mg/d	Medium 300 mg/d	High 600 mg/d
Observed Primary	**5.9**	**5.9**	**9.2**
Observed Secondary	**5.1**	**5.0**	**7.6**
Predicted Slow Washout	**5.4 ± 1.3**	**7.2 ± 1.6**	**8.7 ± 1.6**

Observed difference too big for protective effect alone?

What Happened in ELLDOPA?



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