

# How Drugs May Slow Disease Progression

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## Outline

1. What is Disease Progress?
2. Disease Progress Models
3. Nomenclature
4. Parkinson's Disease Example
5. Washout and Delayed Start Designs

# Clinical Pharmacology

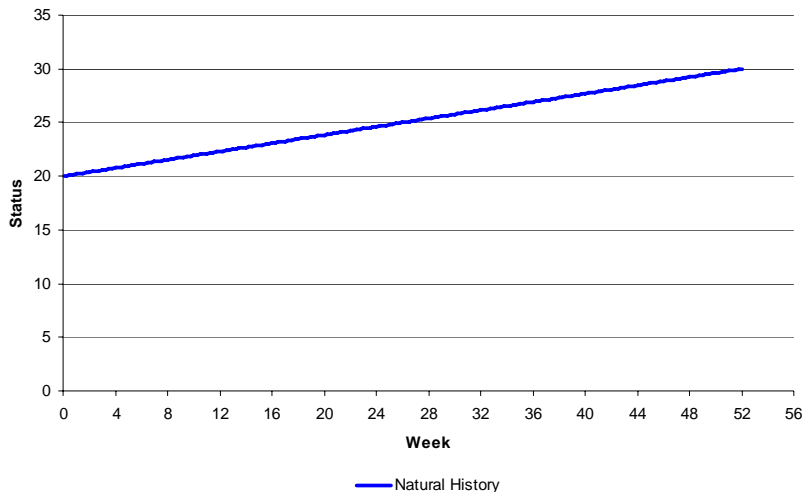
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Disease Progress + Drug Action

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## Linear (Natural History) Disease Progression Model

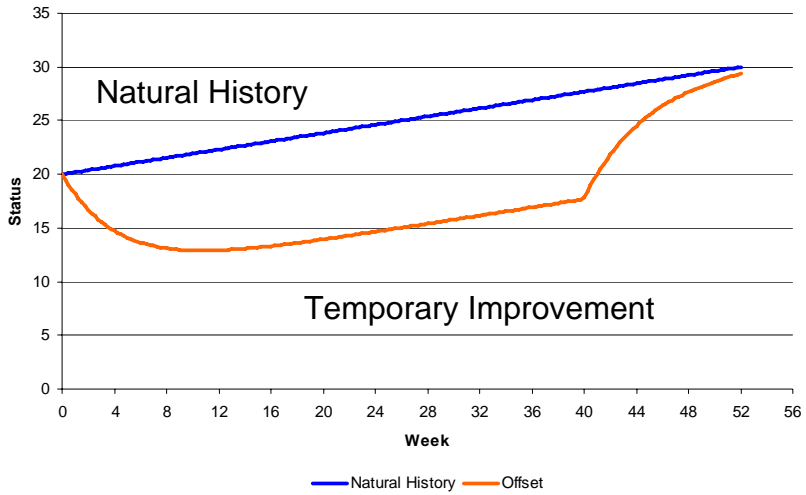
$$S(t) = S_0 + \alpha \cdot t$$



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## Linear + Offset (Symptomatic)

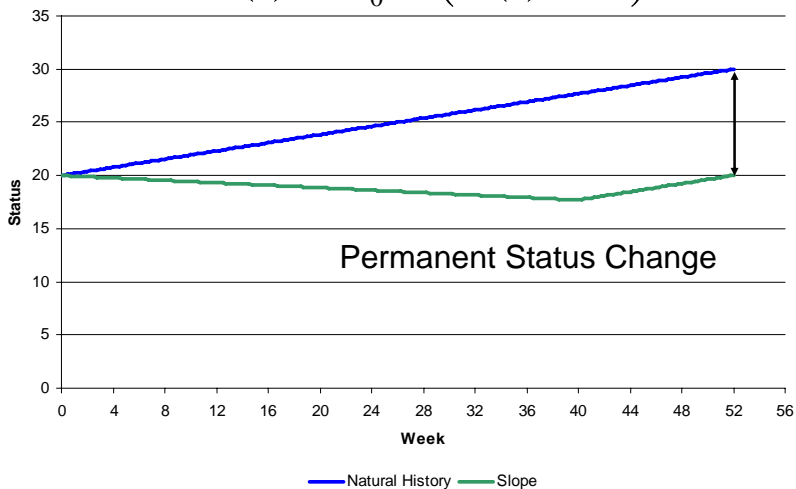
$$S(t) = (S_0 + E(t)) + \alpha \cdot t$$



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## Linear + Slope (Disease Modifying)

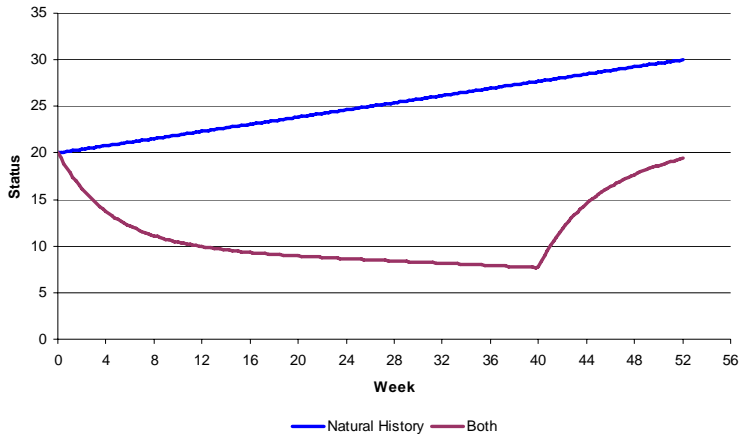
$$S(t) = S_0 + (E(t) + \alpha) \cdot t$$



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## Linear + Offset + Slope Symptomatic and Disease Modifying

$$S(t) = S_0 + E_o(t) + (E_s(t) + \alpha) \cdot t$$



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## Nomenclature

- Symptomatic
  - Equivalent to an additive drug effect on the baseline parameter  $S_0$
  - Synonym is 'offset'
  - Typically delayed onset
  - Rejoins untreated state after washout
- Disease Modifying
  - Drug effect on parameters describing time varying component of natural history
  - Synonym is 'protective' (best used for linear DP models)
  - Typically 'immediate' effect but responses take time to be observable
  - Rejoins untreated state after washout **except** linear disease progress model

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# Parkinson's Disease

## DATATOP Cohort

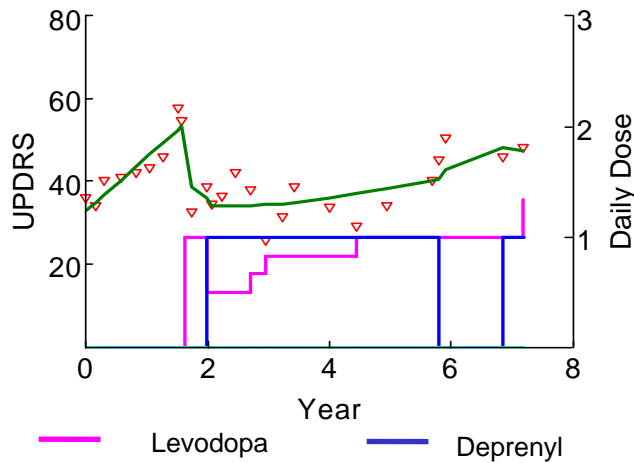
Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism

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

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## Offset + Slope Effect?



Holford NHG, Chan PL, Nutt JG, Kiebertz K, Shoulson I. Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments. J Pharmacokinet Pharmacodyn. 2006 Jun;33(3):281-311

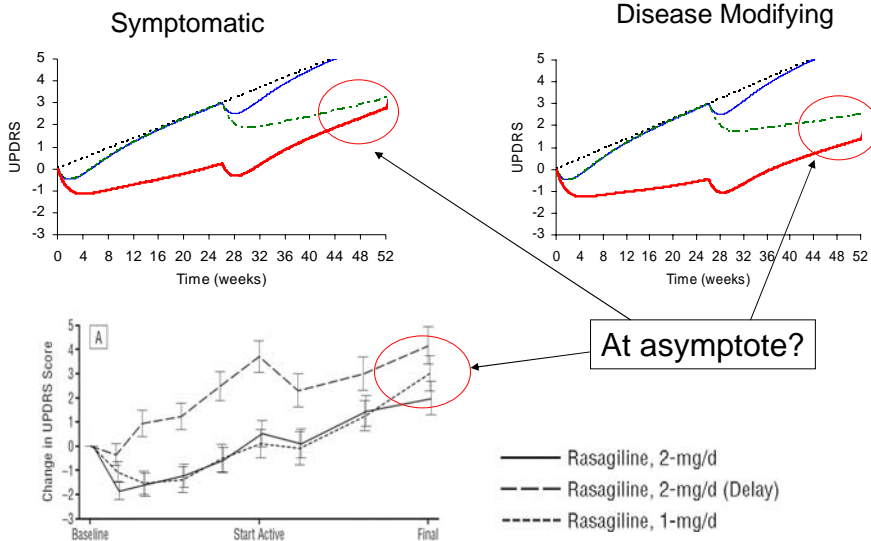
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# Prospective Designs

## Can Disease Modifying Effects be Detected Reliably?

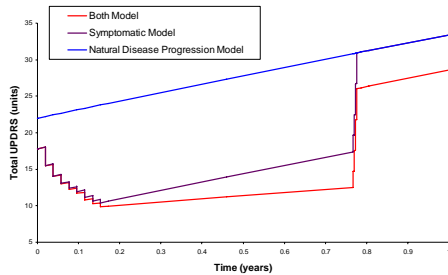
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### TEMPO Delayed Start Design

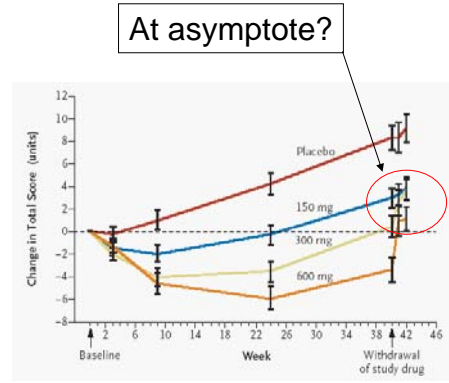


Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. Arch Neurol 2004;61(4):561-6.  
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# ELLDOPA Washout Design



Design



Results

The Parkinson Study Group. Levodopa and the Progression of Parkinson's Disease. N Engl J Med 2004;351(24):2498-2508

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## Do Drugs Modify Disease Progress in Parkinson's?

- Delayed Start and Washout Trials
  - Disease State means inconclusive
  - Time missing from design/analysis
  - Drop outs largely ignored in design stage
  - Naïve assumptions about asymptote
- Second Generation Trials
  - Endpoints are 'Slopes' not Disease State means
  - Time course of progress explicitly included
  - Designs recognize dropout
  - Non-linear model estimates asymptote

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# General References

1. Chan PLS, Holford NHG. Drug treatment effects on disease progression. *Annu Rev Pharmacol Toxicol.* 2001;41:625-59.
2. Holford NHG, Mould DR, Peck CC. Disease Progress Models. In: Atkinson A, editor. *Principles of Clinical Pharmacology.* San Diego: Academic Press; 2001. p. 253-62.
3. Post TM, Freijer JI, DeJongh J, Danhof M. Disease system analysis: basic disease progression models in degenerative disease. *Pharm Res.* 2005 Jul;22(7):1038-49.