

<p>Slide 1</p>	<p style="text-align: center;"><b>Clinical Pharmacology</b></p> <p style="text-align: center;"><b>Disease Progress and Drug Action</b></p> <p style="text-align: center;">Nick Holford Dept Pharmacology and Clinical Pharmacology University of Auckland</p>	
<p>Slide 2</p>	<p style="text-align: center;">Clinical Pharmacology</p> <p style="text-align: center;">=</p> <p style="text-align: center;">Disease Progress + Drug Action</p> <p><small>©NHG Holford, 2020, all rights reserved.</small></p>	<p>Clinical pharmacology can be described as the science of understanding disease progress (clinical) and drug action (pharmacology). Disease progress implies that the disease changes with time. Drug action refers to the time course of drug effect and includes pharmacokinetics, pharmacodynamics and a link model to account for delays in effect in relation to drug concentration. Clinical pharmacology is not a static description of the use of a drug but includes the time course of disease, drug concentration and drug effect.</p>
<p>Slide 3</p>	<p style="text-align: center;"><b>Outline</b></p> <ol style="list-style-type: none"> <li>1. What is disease progress?</li> <li>2. Models for disease progress and drug action</li> <li>3. Parkinson's disease and disease modification</li> </ol> <p><small>©NHG Holford, 2020, all rights reserved.</small></p>	

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## Disease Progress Model

➤ **Quantitative model that accounts for the time course of disease status,  $S(t)$ :**

» **“biomarkers”**

– **Signs** - physiological or biological measurements of disease activity

» **“clinical outcome”**

– **Symptoms** - measure of how a patient feels or functions

– **Survival** - Dead or alive (or had a stroke or not, etc.)

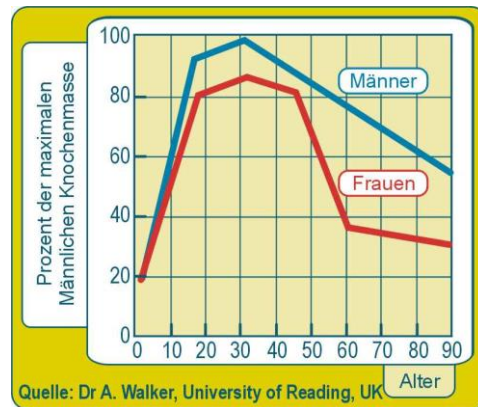
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A symbol to describe disease progress is ‘S’ i.e. the disease status. Disease status is expected to vary with time,  $S(t)$ .

Disease status may be defined in terms of clinical outcomes such as survival and symptoms or in terms of a biomarker. Biomarkers are also known as clinical signs when used by clinicians as diagnostic or prognostic variables.

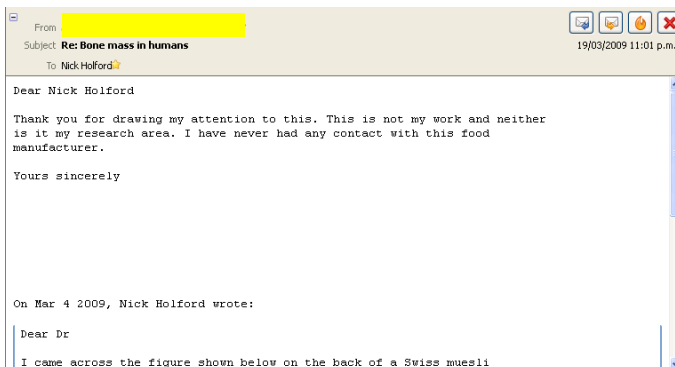
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## Bone Mass in Humans



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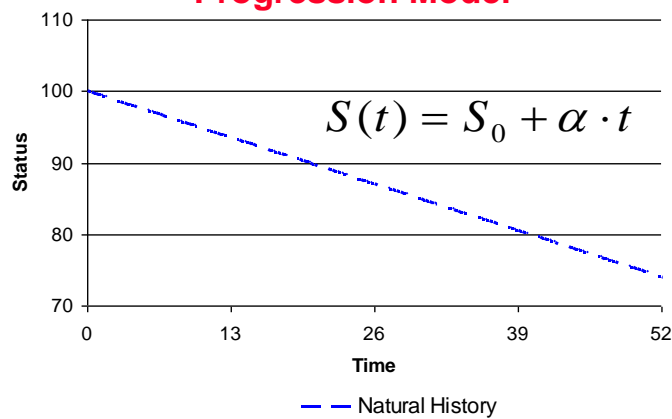
### The Link Between Biomarkers and Outcome Is Well Known



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### Linear (Natural History) Disease Progression Model

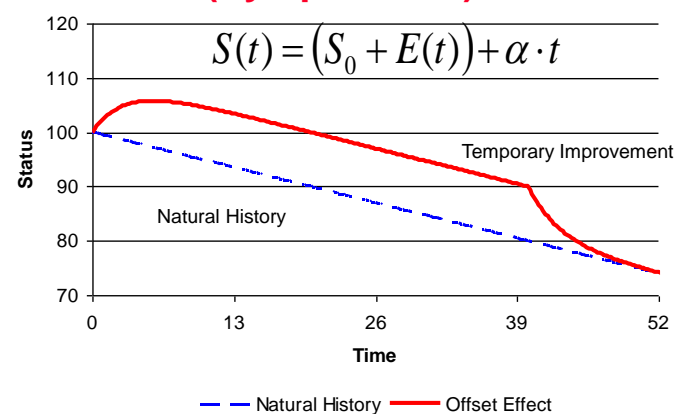


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The simplest model to describe changing disease status with time is linear. In general if the change is relatively small in relation to the time scale of observation then any disease progress curve will reasonably be described by a linear function.

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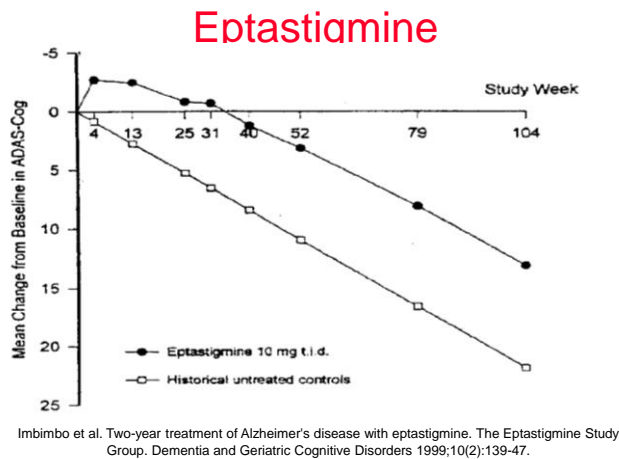
### Linear + Offset (Symptomatic)



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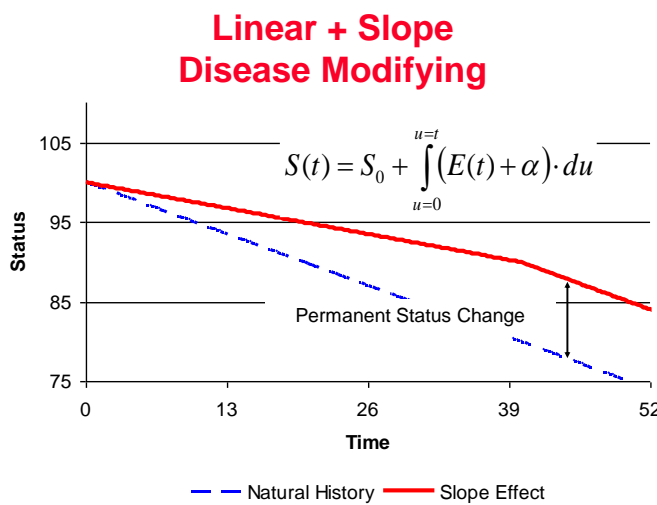
With any disease progress model it is possible to imagine a drug action that is equivalent to a change in the baseline parameter of the model. This kind of effect on disease produces a temporary offset. When treatment is stopped the response to the drug washes out and the status returns to the baseline. In many cases it is reasonable to suppose that the processes governing a delay in onset of drug effect will also affect the loss of effect but the offset effects of levodopa treatment in Parkinson's disease are one exception to this assumption.

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The action of cholinesterase inhibitors in Alzheimer's disease is very similar for all drugs in this class. There is a delayed onset of benefit taking 2 to 3 months to reach its peak followed by continuing progression of the disease at the same rate as expected from natural history progression. This is clear example of an offset type of drug action. If there is a disease modifying effect it is small and hard to detect without withdrawal of treatment.

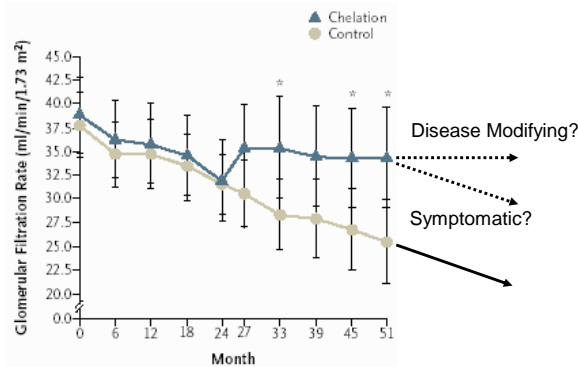
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Drug effects on the slope of a linear model lead to permanent changes in the disease status which are not reversed when treatment is stopped. The persistent change after stopping treatment is the hallmark of a disease modifying action if the natural history is linear.

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### Slow Symptomatic or Disease Modifying?



Lin J-L, Lin-Tan D-T, Kuang-Hong H, Chen-Chen Y. Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. New England Journal of Medicine 2003;348(4):277-286

A trial was undertaken in China in patients with moderate renal functional impairment. After 2 years of follow up they were randomized to treatment with a lead chelating agent. Patients who received chelation treatment had a rapid improvement in function which could be described by an offset effect. There was also a marked slowing of the rate of decline of renal function. This could be described by a slope effect but without washout of treatment it is not possible to distinguish a true disease modifying effect from a slow onset offset effect.

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## Parkinson Study Group DATATOP Cohort

Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism

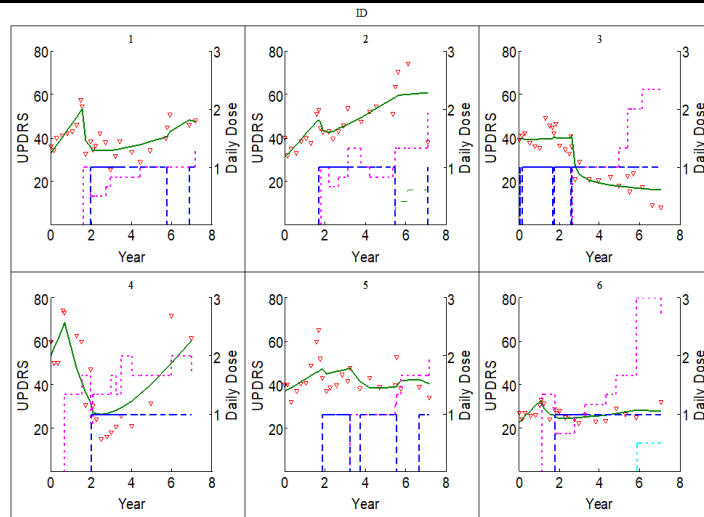
PKPD of anti-parkinsonian treatment  
and Parkinson's disease over 7 years  
in 800 patients

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

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The DATATOP study was performed over 2 year period but patients enrolled in the study were subsequently followed up for 8 years. The time course of disease status in Parkinson's disease and the effects of treatment were described by a disease progress model. The NM-TRAN code for this analysis can be found in Holford et al. 2006. 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 Pharmacokinetic Pharmacodyn. 2006 Jun;33(3):281-311.

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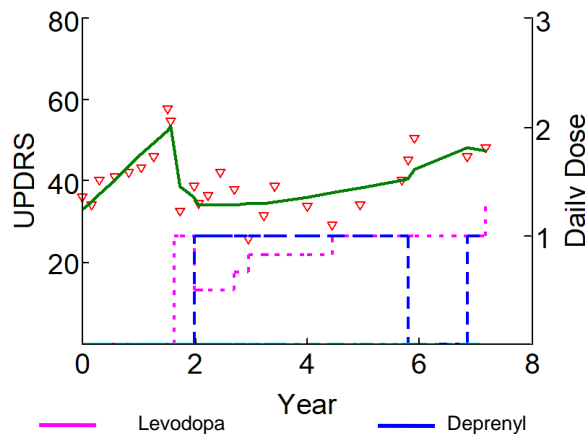


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Disease status was followed with the Unified Parkinson's Disease Response Scale (UPDRS). The UPDRS patterns were quite variable from patient to patient. A major source of variability was the response to individual drug treatments.

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### Symptomatic plus Disease Modifying?

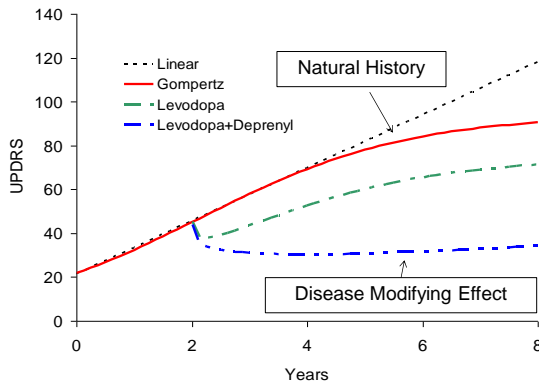


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The first patient in the DATATOP cohort shows the patterns that were eventually used to build a disease progress and drug action model. The initial rate of progression seems to be slowed when treatment with levodopa and deprenyl is used. In addition there is a marked symptomatic effect which is primarily attributable to levodopa. It is not obvious what disease progress model is most suitable but it could be linear. Testing different model led to the conclusion that the disease progress approached an asymptote using a Gompertz model.

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### Combined Effects of Levodopa and Deprenyl

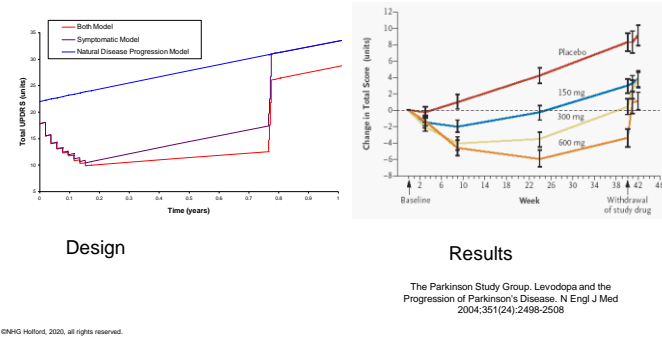


Holford NHG, Chan PL, Nutt JG, Kieburtz K, Shoulson I. Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments. J Pharmacokinet Pharmacodyn. 2006;33(3):281-311. ©NHG Holford, 2020, all rights reserved.

The effects of levodopa and deprenyl are shown. Both have offset effects and protective effects which was described by an action on the time constant of a Gompertz asymptotic model. See Holford et al 2006 for details of the model code. Holford NHG, Chan PL, Nutt JG, Kieburtz K, Shoulson I. Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments. J Pharmacokinet Pharmacodyn. 2006;33(3):281-311.

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### ELLDOPA Before and After



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The Parkinson Study Group which performed the DATATOP study was interested in asking if levodopa changes the rate of progression of Parkinson's disease. They designed a trial that was simple in principle but it rested on a key assumption that symptomatic effects of levodopa would wash out within 2 weeks of stopping treatment. When treatment was stopped after 9 months there was a loss of UPDRS response over the next 2 weeks but it did not approach the response seen in a parallel placebo treated group. The marked difference from placebo could be due to a true disease modifying effect or a very slow loss of symptomatic effect.

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### ELLDOPA predicted from DATATOP Model

UPDRS total Mean Difference from Placebo at Week 42  
Predictions from clinical trial simulation (100 replicates)  
Differences are Average ± SE

	Low 150 mg/d	Medium 300 mg/d	High 600 mg/d
<b>Observed Difference</b>	5.9 ± 1.2	5.9 ± 1.3	9.2 ± 1.3
<b>Predicted Difference</b>	3.8 ± 1.4	5.9 ± 1.3	8.4 ± 1.3

The Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004 December 9, 2004;351(24):2498-508.

Chan PL, Nutt JG, Holford NH. Levodopa slows progression of Parkinson's disease. External validation by clinical trial simulation. Pharm Res. 2007 Apr;24(4):791-802.

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The ELLDOPA study was prospectively simulated using the model for disease progress and levodopa effects obtained from the DATATOP cohort. The predicted difference from placebo in three levodopa dose groups was very similar to the observed response. This is a form of external validation of the DATATOP model. This is a very strong test of the value of the model developed from DATATOP because it predicted the outcome of a trial with a very different design.

Chan PL, Nutt JG, Holford NH. Levodopa slows progression of Parkinson's disease. External validation by clinical trial simulation. Pharm Res. 2007 Apr;24(4):791-802.

## What Did We Learn?

- **Disease Progression**
  - » Understand the time course of the natural history
  - » Often simple descriptions can be used
  - » Straight lines work for small changes
  
- **Drug Action**
  - » **Offset** -- almost always delayed
    - Symptomatic most common
  - » **Slope** -- disease modifying
    - Few examples but confirmed for levodopa and deprenyl in Parkinson's disease